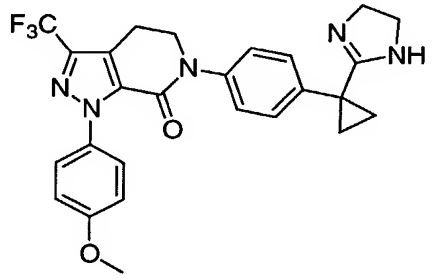
mmol) were then added and the reaction was heated to 120°C for 12 h under an environment of N_2. The reaction was cooled, diluted with EtOAc, washed with H_2O (2x), brine, dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(4,5-dihydro-oxazol-2-yl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester. LC/MS (ESI$^+$) 501.8 $(M+H)^+$, t_R=2.64 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from Part A (0.10 g, 0.20 mmol) was dissolved in ethylene glycol saturated with ammonia (2.0 mL) and heated to 85°C for 4 h. Reaction was cooled, diluted with H_2O, and washed with EtOAc (3x). Organic portions were combined and washed with brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness. The title compound was recrystalized from EtOAc/Hexanes (0.03 g, yield: 32%). LC/MS (ESI$^+$) 472.6 $(M+H)^+$, t_R=1.49 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (CD_3OD) δ 7.47 (d, *J*=9.2 Hz, 2H), 7.38 (AA'BB', *J*=8.5 Hz, 4H), 4.86 (t, 2H), 4.25 (t, 2H), 3.81 (s, 3H), 3.72 (t, 2H), 1.49 (m, 2H), 1.16 (m, 2H) ppm.

Example 144

6-{4-[1-(4,5-Dihydro-1*H*-imidazol-2-yl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Part A. 1-(4-Iodo-phenyl)-cyclopropanecarboxylic acid (0.99 g, 3.4 mmol), DCC (0.71 g, 3.4 mmol), and pentafluorophenol

(0.91 g, 4.9 mmol) were added into CH_2Cl_2 (6 mL) and allowed to stir for 2 h. Piperidine (0.7 mL, 7.1 mmol) was then added dropwise to the slurry. Reaction was allowed to stir for an additional 12 h. The reaction was then diluted with EtOAc; filtered; washed with 1N HCl, 1N NaOH (2x), and brine; dried over $MgSO_4$; filtered; and concentrated to dryness. The crude mixture was purified by flash chromatography (silica, EtOAc:hexanes (3:1) to give [1-(4-iodo-phenyl)-cyclopropyl]-piperidin-1-yl-methanone (1.09, yield: 88%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.4 Hz, 2H), 3.55 (bs, 2H), 3.67 (bs, 2H), 1.60, (bs, 2H), 1.54 (bs, 2H), 1.41 (m, 2H), 1.25 (bs, 2H), 1.13 (m, 2H) ppm.

Part B. The product from part A (1.09 g, 3.03 mmol) was dissolved in toluene (10.0 mL) and [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (0.9 g, 2.2 mmol) was added. The reaction was heated to 90°C for 1.5 h and cooled. An additional 0.5 g (1.23 mmol) of [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] was added and heated for 12 h. The reaction mixture was concentrated and purified via flash chromatography (silica, EtOAc:Hexanes=3:1) to yield [1-(4-Iodo-phenyl)-cyclopropyl]-piperidin-1-yl-methanethione (0.92 g, yield: 88%). LC/MS (ESI^+) 372.0 $(M+H)^+$, t_R=6.56 min (5-98% CH_3CN/H_2O in a 10-min run).

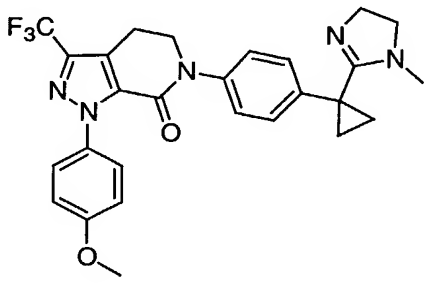
Part C. The product from Part B (0.92 g, 2.4 mmol) was treated with neat methyl iodide (2.00 mL, 32.1 mmol) at rt and allowed to stir under N_2 for 48 h. The reaction was concentrated and stripped (3x) with methanol to provide a yellow solid of 1-{[1-(4-iodo-phenyl)-cyclopropyl]-methylsulfanyl-methylene}-piperidinium; iodide (0.51 g, yield: 41%).

Part D. The product from Part C (0.51 g, 0.99 mmol) was dissolved in methanol (3.0 mL) and ethylenediamine (0.1 mL, 1.49 mmol) was added dropwise at rt. After 2h, reaction mixture was concentrated to dryness and purified via flash chromatography (silica, 100% EtOAc, then 0.5% Et_3N:10% MeOH:CH_2Cl_2) to yield 2-[1-(4-iodo-phenyl)-cyclopropyl]-4,5-dihydro-1H-imidazole (0.20 g, yield: 66%). ^1H NMR (CD_3OD, 300 MHz) δ 7.68 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.5 Hz, 2H), 3.61 (s, 4H), 1.48 m, 2H), 1.25 (s, 2H) ppm.

Part E. The product from Part D (0.093 g, 0.298 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.096 g, 0.309 mmol) and 2-[1-(4-iodo-phenyl)-cyclopropyl]-4,5-dihydro-1H-imidazole (0.093 g, 0.298 mmol) were coupled by the usual procedure. Purification was accomplished using flash chromatography (silica, 100% EtOAc then 0.5% Et_3N:10% MeOH:CH_2Cl_2) to give product (35 mg, yield: 38%). LC/MS (ESI^+) 496.6 $(M+H)^+$, t_R=2.16 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (CD_3OD, 300 MHz) δ 7.47 (AA'BB', *J*=8.6 Hz, 4H), 7.30 (d, *J*=8.4 Hz, 2H), 6.98 (d, *J*=9.1 Hz, 2H), 4.11 (t, *J*=6.6 Hz, 2H) 3.82 (s, 3H), 3.52 (s, 4H), 3.15 (t, *J*=6.6 Hz, 2H), 1.44 (m, 2H), 1.16 (m, 2H) ppm.

Example 145

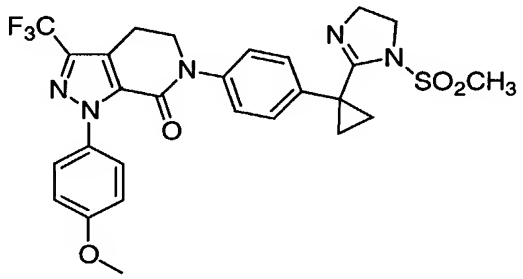
1-(4-Methoxyphenyl)-6-{4-[1-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



The title compound was obtained following the same sequence as those in Example 145 but using N-methylethylenediamine instead of ethylene diamine. LC/MS (ESI$^+$) 510.6 (M+H)$^+$, t_R=2.75 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (CD_3Cl_3, 300 MHz) δ 7.45 (d, *J*=8.8 Hz, 2H), 7.27 (m, 4H), 6.92 (d, *J*=9.2 Hz, 4H), 4.12 (m, 2H), 3.85 (m, 2H), 3.81 (s, 3H), 3.16 (t, *J*=6.6 Hz, 2H), 2.89 (s, br, 3H), 1.59 (m, 2H), 1.28 (m, 2H) ppm.

Example 146

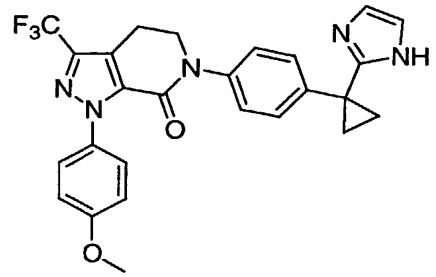
6-{4-[1-(1-Methanesulfonyl-4,5-dihydro-1*H*-imidazol-2-yl)-cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



The product from Example 144 (0.017 g, 0.034 mmol) from was dissolved in CH_2Cl_2 (0.3 mL). Et_3N (0.01mL, 0.07 mmol) and MsCl (0.07 mL, 0.09 mmol) were added at rt under N_2. The reaction was stirred for 12 h, concentrated to dryness, and purified via flash chromatography (silica, 100% EtOAc then 0.5% Et_3N:10% MeOH:CH_2Cl_2) to afford the title compound. LC/MS (ESI$^+$) 574.4 (M+H)$^+$, t_R=2.84 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($(CD_3)_2CO$, 300 MHz) δ 7.50 (d, *J*=9.1 Hz, 2H), 7.33 (m, 4H), 6.98 (d, *J*=9.1 Hz, 2H), 4.16 (t, *J*=6.6 Hz, 2H), 3.83 (m, 7H), 3.16 (t, *J*=6.4 Hz, 2H), 2.42 (s, 3H), 1.47 (m, 2H), 1.18 (m, 2H) ppm.

Example 147

6-{4-[1-(1*H*-Imidazol-2-yl)cyclopropyl]phenyl}-1-(4-methoxy-phenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



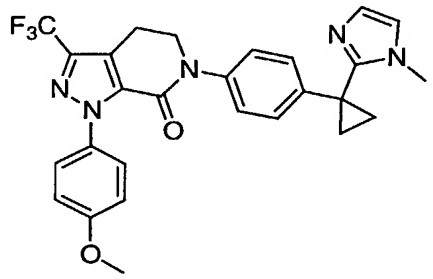
Part A. H-(Boc)-DAP-OMe was dissolved in CH_2Cl_2 (2.0 mL) and TFA (1.0 mL) was added. The reaction was allowed to stir for 2h. The reaction was concentrated and stripped with $CHCl_3$ (10 mL x 3). The reaction mixture was re-diluted with MeOH (6.0 mL) and K_2CO_3 (spatula tip) added. The product from Part C in Example 142 (0.12 g, 0.234 mmol) was added and the reaction was heated to 65°C for 2h. The reaction was concentrated and purified via flash chromatography (silica, EtOAc-10% MeOH/CH_2Cl_2) to afford 2-[1-(4-Iodo-phenyl)-cyclopropyl]-4,5-dihydro-3H-imidazole-4-carboxylic acid methyl ester. LC/MS (ESI$^+$) 371.0 $(M+H)^+$, t_R=2.17 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. 1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (45.0 mg, 0.145 mmol) and product from Part A (36.0 mg, 0.098 mmol) were dissolved in DMSO (0.5 mL). K_2CO_3 (10.0 mg, 0.723 mmol) was added followed by 1,10-phenanthroline (spatula tip) and copper iodide (spatula tip). The reaction was heated to 110°C for 12 h. The reaction was diluted with EtOAc and washed with H_2O (2x) and brine. Organic was dried over $NaSO_4$, filtered, and concentrated. The reaction was purified via flash chromatography (silica, EtOAc-10% MeOH/1% EtN_3/CH_2Cl_2). Side product obtained from loss of

CO_2Me under the basic conditions to form the title compound. LC/MS (ESI^+) 494.2 $(M+H)^+$, t_R=2.21 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($(CD_3)_2CO$, 300 MHz) δ 7.50 (d, *J*=9.2 Hz, 2H), 7.32 (m, 4 H), 6.98 (d, *J*=9.1 Hz, 2H), 6.83 (s, 2H), 4.16 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 3.16 (t, *J*=6.2 Hz, 2H), 1.47 (m, 2H), 1.18 (m, 2H) ppm.

Example 148

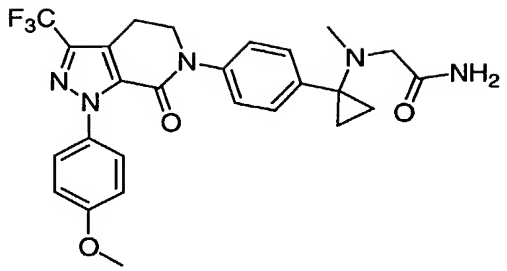
1-(4-Methoxyphenyl)-6-{4-[1-(1-methyl-1*H*-imidazol-2-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



The product from Example 144 (0.08 g, 0.18 mmol) was dissolved in 1,4-dioxane (2.0 mL) and $KMnO_4$ (spatula tip) was added. The reaction was heated to 80°C for 12 h at rt. The reaction was filtered, concentrated, and purified via flash chromatography (silica, 100% EtOAc then 0.5% Et_3N:10% $MeOH/CH_2Cl_2$ then 100% MeOH) to yield the title compound (0.06 g, yield: 72%). ^1H NMR δ 7.44 (d, *J*=9.1 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H), 6.98 (m, 4H), 4.07 (dd, *J*=2.9, 3.7 Hz, 2H), 3.81 (s, 3H), 3.48 (s, 2H), 3.12 (t, *J*=6.2 Hz, 2H), 1.44 (m, 2H), 1.21 (t, *J*=7.3 Hz, 2H) ppm.

Example 149

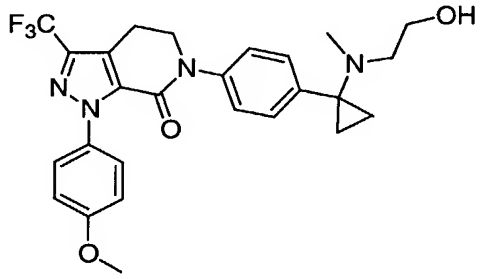
2-[(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-methyl-amino]-acetamide



The product of Example 130 (50 mg, 0.11 mmmol) was stirred in DMF (0.3 mL). K_2CO_3 (45 mg, mmol, 0.33 mmol, 3 eq) and chloroacetamide (20 mg, 0.21 mmol, 2 eq) were added. The mixture was stirred at 70°C for 2h. EtOAc was added, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by Silica gel purification to yield the title compound. LC/MS (ESI^+) 514.8 $(M+H)^+$, t_R=2.00 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ7.46 (d, J=9.2 Hz, 2H), 7.27 (m, 4H), 6.91 (d, J=8.8 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.15 (m, 4H), 2.29 (m, 3H), 0.97 (m, 2H), 0.87 (m, 2H) ppm.

Example 150

6-(4-{1-[(2-Hydroxyethyl)-methylamino]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one

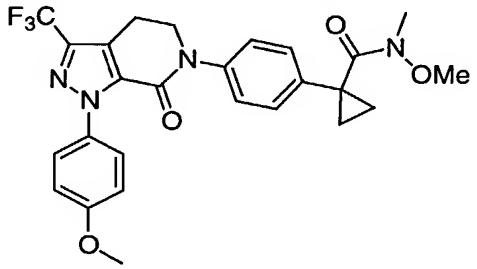


Following a procedure analogous to that used for the preparation of Example 149 but using 2-bromoethanol instead, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI^+) 501.8 $(M+H)^+$, t_R=2.04 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ7.46 (d, J=9.1 Hz, 2H), 7.29 (m,

4H), 6.92 (d, *J*=8.8, 2H), 4.14 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.51 (m, 2H), 3.16 (t, *J*=6.6 Hz, 2H), 2.64 (m, 2H), 2.23 (s, 3H), 0.95 (s, 3H), 0.83 (m, 2H) ppm.

Example 151

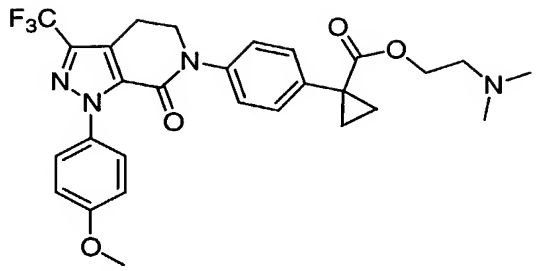
1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropanecarboxylic acid methoxy-methyl-amide



1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}cyclopropane carboxylic acid (1.12 g, 2.37 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.255 g, 2.61 mmol) were dissolved in DMF (20.0 mL) and DIEA (2.0 mL, 11.5 mmol)was added dropwise. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.54 g, 2.8 mmol) was added and the reaction was allowed to proceed under nitrogen at rt for 12 h. The reaction was diluted with EtOAc, washed 1N HCl, brine, dried over Na_2SO_4, filtered and concentrated. The reaction was purified via flash chromatography (silica, 100% EtOAc, then 10% MeOH/CH_2Cl_2) to give the title compound. LC/MS (ESI^+) 515.6 (M+H).

Example 152

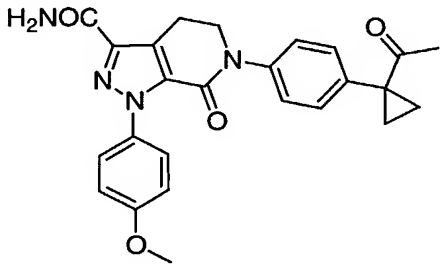
6-[4-(1-Hydroxymethylcyclopropyl)phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide



The title compound was obtained as a side product in the reaction from Example 151 (0.55 g, 0.96 mmol) was obtained in 40% yield. LC/MS (ESI$^+$) 556.4 (M+H)$^+$, t_R=1.77 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.50 (d, *J*=8.8 Hz, 2H), 7.39 (AA'BB', *J*=8.8 Hz, 4H), 7.01 (d, *J*=8.8 Hz, 2H), 4.19 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 3.76 (m, 2H), 3.20 (m, 4H), 2.85 (s, 3H), 2.63 (s, 6H), 1.52 (m, 2H), 1.31 (m, 2H), 1.09 (t, *J*=7.0 Hz, 2H), 0.81 (t, *J*=6 Hz, 1H) ppm.

Example 153

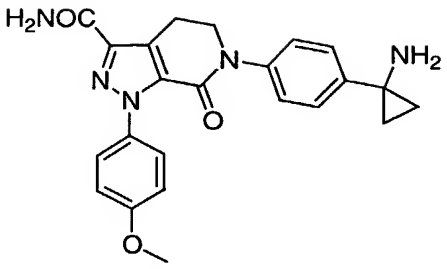
6-[4-(1-Acetyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used in Example 138, the title compound was prepared. LC/MS (ESI$^+$) 445.6 (M+H).

Example 154

6-[4-(1-Aminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Part A. [1-(4-Iodo-phenyl)-cyclopropyl]-carbamic acid tert-butyl ester (0.34 g, 0.95 mmol) and 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.30 g, 0.97 mmol) were stirred in DMSO (1 mL). K_2CO_3 (0.25 g, 1.81 mmol), CuI (87 mg, 0.46 mmol) and 1,10-phenanthroline (83 mg, 0.46 mmol) were added. The resulting mixture was heated at 120°C for 2.5 h. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2:EtOAc=1:1, then EtOAc) to give 6-[4-(1-tert-butoxycarbonylamino-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.24 g, yield: 46%).

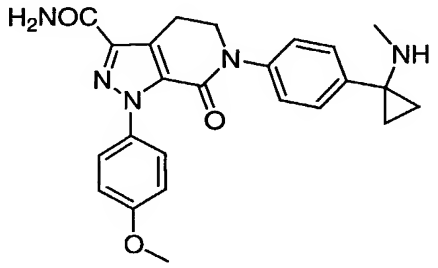
Part B. The product from Part A underwent the same reaction as used in Part E of Example 67 to yield (1-{4-[3-carbamoyl-1-(4-methoxy-phenyl)-7-oxo-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-carbamic acid tert-butyl ester. HRMS $C_{28}H_{32}N_5O_5$ $(M+H)^+$ 518.2388 calcd for 518.2325. ^1H NMR ($CDCl_3$) δ 7.47 (d, J=9.2 Hz, 2H), 7.23 (m, 4H), 6.93 (d, J=9.1 Hz, 2H), 6.85 (s, br, 1H), 5.52 (s, br, 1H), 5.26 (s, br, 1H), 4.08 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.36 (t, J=6.6 Hz, 2H), 1.42 (s, br, 9H), 1.24 (m, 2H), 1.18 (m, 2H) ppm.

Part C. The product from Part B (54 mg, 0.104 mmol) was stirred in CH_2CL_2 (2 mL) and TFA (1 mL) at rt for 30 min.

After evaporation, the residue was purified by reverse phase HPLC to afford the title compound (40 mg, yield: 91.7%). HRMS $C_{23}H_{23}N_5O_3$ $(M+H)^+$ 418.1908 calcd for 418.1879.

Example 155

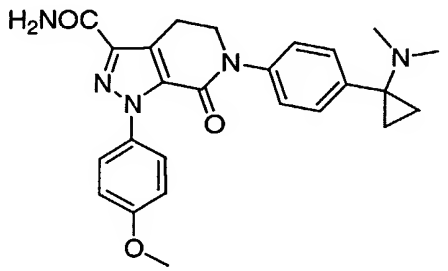
1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)-phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 166, the title compound was prepared. LC/MS (ESI^+) 432.6 $(M+H)^+$, t_R=1.74 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (acetone-d_6) δ 7.65 (d, J=8.5 Hz, 2H), 7.49 (m, 4H), 7.33 (s, br, 1H), 6.97 (d, J=9.2 Hz, 2H), 6.74 (s, br, 1H), 5.69 (s, 1H), 4.15 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.28 (t, J=6.6 Hz, 2H), 2.63 (s, 3H), 1.63 (m, 2H), 1.19 (m, 2H) ppm.

Example 156

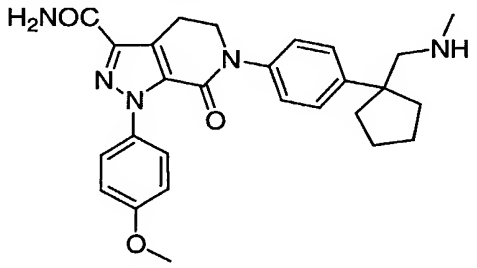
6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



The product of Example 154, HOAc (0.05 mL), and aqueous paraformaldehyde (0.3 mL) were stirred in CH_3CN (1.5 mL) at rt for 15 min. $NaBH_3CN$ (60 mg) was added. The mixture was stirred at rt for 2h. H_2O was added. The organic solvent was evaporated. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). HRMS $C_{25}H_{28}N_5O_3$ $(M+H)^+$ 446.2178 calcd for 446.2193. ^1H NMR (acetone-d_6) δ 7.67 (d, J=8.4 Hz, 2H), 7.51 (AA'BB', J=8.8 Hz, 4H), 6.98 (d, J=9.1 Hz, 2H), 4.17 (t, J=6.6 Hz, 2H), 3.83 (s, 3H), 3.29 (t, J=6.6 Hz, 2H), 2.77 (s, 6H), 1.67 (m, 2H), 1.15 (m, 2H) ppm.

Example 157

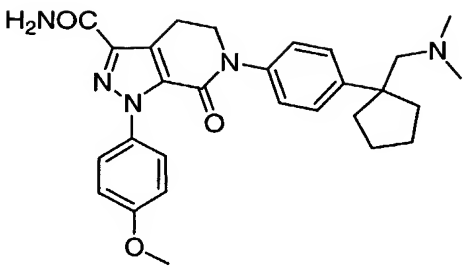
6-[4-(1-Methylaminomethylcyclopentyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following an analogous procedures as those used in Examples 27 and 67, the title compound was prepared. HRMS $C_{27}H_{32}N_5O_3$ $(M+H)^+$ 474.2533 calcd for 474.2506.

Example 158

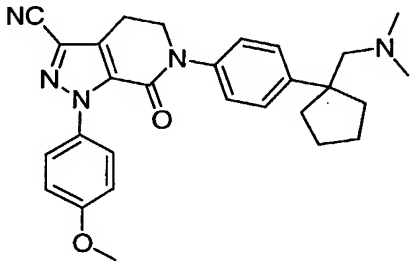
6-[4-(1-Dimethylaminomethylcyclopentyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following an analogous procedures as those used in Examples 28 and 68, the title compound was prepared. LC/MS (ESI^+) 488.6 $(M+H)^+$, t_R=1.77 min (10-90% CH_3CN/H_2O in a 4-min run).

Example 159

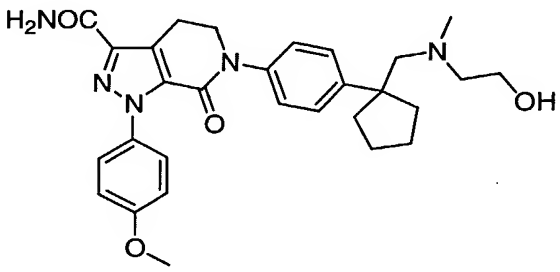
6-[4-(1-Dimethylaminomethylcyclopentyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following an analogous procedures as those used in Examples 28 and 75, the title compound was prepared. HRMS $C_{28}H_{32}N_5O_3$ $(M+H)^+$ 470.2577 calcd for 470.2557.

Example 160

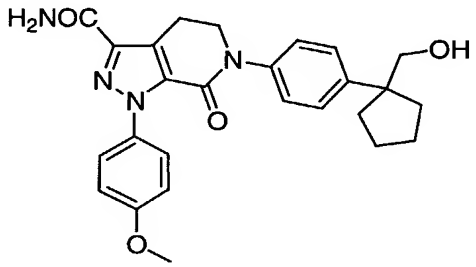
6-[4-(1-[(2-Hydroxyethyl)methylaminomethyl]-cyclopentyl)phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 150 but using the product of Example 157 as the starting material, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 518.8 (M+H). ^1H NMR (acetone-d_6) δ 7.56 (d, J=8.8 Hz, 2H), 7.51 (d, J=9.1 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H), 6.97 (d, J=9.2 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.78 (m, 2H), 3.69 (m, 2H), 3.27 (t, J=6.6 Hz, 2H), 3.15 (t, J=5.0 Hz, 2H), 2.60 (s, 3H), 2.17 (m, 4H), 1.81 (m, 2H), 1.64 (m, 2H) ppm.

Example 161

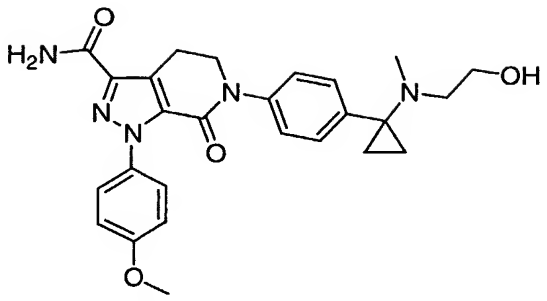
6-[4-(1-Hydroxymethyl-cyclopentyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used in Example 95, the title compound was prepared. LC/MS (ESI^+) 461.4.

Example 162

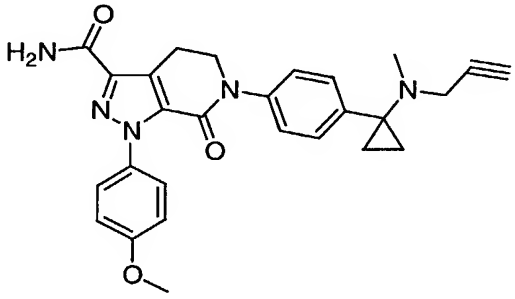
6-(4-{1-[(2-Hydroxyethyl)methylamino]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 150 but using the product of Example 155 as the starting material, the title compound was prepared. HRMS $C_{26}H_{30}N_5O_4$ $(M+H)^+$ 476.2299 calcd for 476.2319.

Example 163

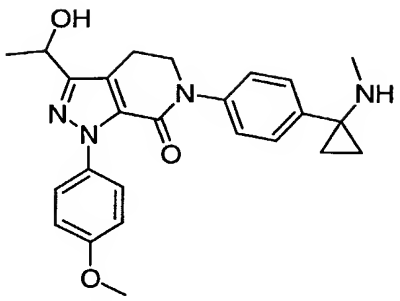
1-(4-Methoxyphenyl)-6-{4-[1-(methyl-prop-2-ynylamino)-cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 162 but using 3-bromo-propyne as the starting material instead of 2-bromoethanol, the title compound was prepared. HRMS $C_{27}H_{28}N_5O_3$ $(M+H)^+$ 470.2178 calcd for 470.2193.

Example 164

3-(1-Hydroxyethyl)-1-(4-methoxyphenyl)-6-[4-(1-methylamino-cyclopropyl)phenyl]-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



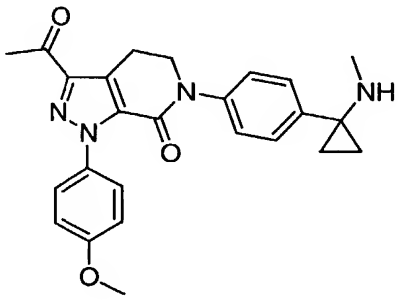
Part A. 6-{4-[1-(tert-Butoxycarbonyl-methyl-amino)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.59 g, 1.79 mmol) was stirred in EtOH (15 mL) and 1N NaOH (3 mL) at rt for 1h. After evaporation, the mixture was acidified with citric acid. The mixture was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo. This acid underwent a series of reactions similar to those used in Part E of Example 1 to afford (1-{4-[3-formyl-1-(4-methoxy-phenyl)-7-oxo-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-methyl-carbamic acid tert-butyl ester (yield: 99%). LC/MS (ESI^+) 461.6 $(M+H-t\text{-}Bu)^+$, t_R=1.2.97 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from Part A (0.38 g, 0.74 mmol) was stirred in CH_2Cl_2 (6 mL) at -78°C under N_2. $ZnMe_2$ (2M in toluene, 0.74 mL, 1.48 mmol) was added dropwise followed by the addition of $TiCl_4$ (0.16 mL, 1.07 mmol) dropwise. The reaction was stirred at -78°C for 2h. Saturated NH_4Cl was added. The mixture was extracted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by FCC (silica gel, CH_2Cl_2, then 20% EtOAc in CH_2Cl_2) to yield (1-{4-[3-(1-hydroxy-ethyl)-1-(4-methoxy-phenyl)-7-oxo-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-methyl-carbamic acid tert-butyl ester (81 mg, yield: 25%). HRMS $C_{26}H_{30}N_5O_4$ $(M+H)^+$ 533.2778 calcd for 533.2765.

Part C. The product from Part B (10 mg) was stirred in CH_2Cl_2 (1 mL) and TFA (1 mL) at rt for 30 min. After evaporation, the residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O) to afford the title compound. HRMS $C_{26}H_{30}N_5O_4$ $(M+H)^+$ 433.2247 calcd for 433.2240. ^1H NMR (CD_3OD) δ 7.59 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 6.94 (d, *J*=8.4 Hz, 2H), 5.00 (q, *J*=6.6 Hz, 1H), 4.10 (m, 2H), 3.83 (s, 3H), 3.15 (t, *J*=6.6 Hz, 2H), 2.58 (s, 3H), 1.56 (d, *J*=8.4 Hz, 4H), 1.39 (m, 2H), 1.28 (m, 2H) ppm. ^{19}F NMR (CD_3OD) δ -77.49 ppm.

Example 165

3-Acetyl-1-(4-methoxyphenyl)-6-[4-(1-methylamino-cyclopropyl)phenyl]-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

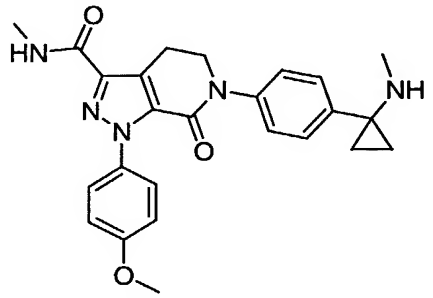


The product from Part B in Example 164 (50 mg, 0.094 mmol), PCC (40 mg, 0.19 mmol), NaOAc (23 mg, 0.28 mmol), and 4Å MS (50 mg) were stirred in CH_2Cl_2 (1 mL) for 4h. The mixture was filtered through Celite®, washed with H_2O (2x), dried over $MgSO_4$, filtered and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (4 mL) and TFA (2 mL) at rt for 30 min. After evaporation, the residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O) to afford the title compound. ^1H NMR (CD_3OD) δ 7.59 (d, *J*=8.1 Hz, 2H), 7.46 (m, 4H), 6.98 (d, *J*=9.1 Hz, 2H), 4.11 (t, *J*=6.6 Hz, 2H), 3.82 (m, 5H), 3.29 (m, 2H), 2.59 (m, 3H), 1.39 (m, 2H), 1.28 (m,

2H) ppm. ^{19}F NMR (CD_3OD) δ -77.51 ppm. HRMS $C_{25}H_{27}N_4O_3$ $(M+H)^+$ 431.2102 calcd for 431.2084.

Example 166

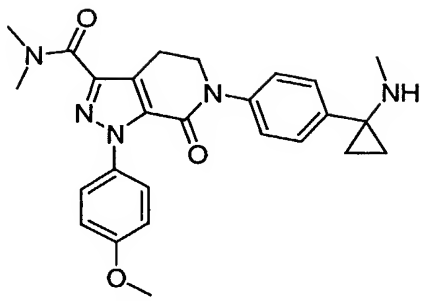
1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid methylamide, trifluoroacetic acid salt



The product from Part A in Example 164 (0.21 g, 0.44 mmol) was stirred in CH_2Cl_2 (5 mL) at 0°C. $(COCl)_2$ (0.1 mL) was added followed by the addition of 1 drop of DMF. The mixture was stirred at 0°C for 40 min. The solvents were evaporated in vacuo. Half of the residue was dissolved in CH_2Cl_2 (1 mL) and $MeNH_2$ (2 M in THF, 0.5 mL) was added. The mixture was stirred at rt for 4h. The solvents were evaporated. The residue was dissolved in CH_2Cl_2 (15 mL) and TFA (2 mL). The mixture was stirred at rt for 1h. The solvents were evaporated. The residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA) and lyophilized to dryness. HRMS $C_{25}H_{28}N_5O_3$ $(M+H)^+$ 446.2177 calcd for 446.2193. ^1H NMR (CD_3OD) δ 7.59 (d, *J*=9.1 Hz, 2H), 7.47 (m, 4H), 6.96 (d, *J*=9.1 Hz, 2H), 4.17 (t, *J*=6.6 Hz, 2H), 3.82 (m, 5H), 3.29 (m, 2H), 3.17 (m, 2H), 2.92 (m, 3H), 1.61 (m, 2H), 1.34 (m, 2H) ppm.

Example 167

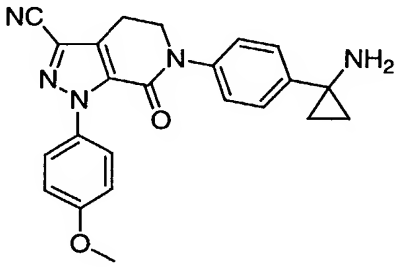
1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid dimethylamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 166 but using dimethylamine as the starting material, the title compound was prepared. The product was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA) and lyophilized to dryness. HRMS $C_{26}H_{30}O_3N_5$ $(M+H)^+$ 460.2319 calcd for 460.2349. ^1H NMR (CD_3OD) δ 7.59 (m, 2H), 7.45 (m, 4H), 6.96 (m, 2H), 4.11 (t, *J*=6.6 Hz, 2H), 3.37 (s, 3H), 3.17 (t, *J*=6.6 Hz, 2H), 3.12 (s, 3H), 2.59 (s, 3H), 1.39 (m, 2H), 1.29 (m, 2H) ppm. ^{19}F NMR (CD_3OD) δ -77.56 ppm.

Example 168

6-[4-(1-Aminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt

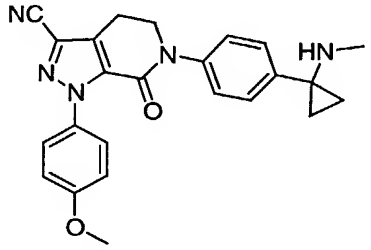


Following a procedure analogous to that used in Example 74 but using the product of Example 154 as the starting material, the title compound was prepared. The product was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA) and lyophilized to dryness. LC/MS(ESI^+) 400.4 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.52 (d, *J*=9.1 Hz, 2H), 7.41 (AA'BB', *J*=8.0 Hz, 4H), 6.98 (d, *J*=9.1 Hz, 2H), 4.19 (t,

J=6.6 Hz, 2H), 3.83 (s, 3H), 3.20 (t, *J*=6.6 Hz, 2H), 1.69 (m, 2H), 1.51 (m, 2H) ppm.

Example 169

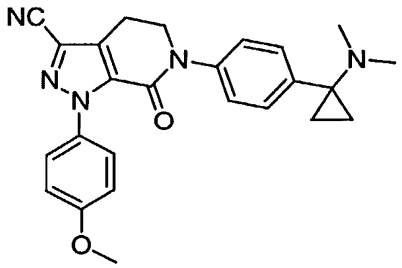
1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74 but using the product of Example 155 as the starting material, the title compound was prepared. HRMS $C_{24}H_{24}O_2N_5$ $(M+H)^+$ 414.1900 calcd for 414.1931. ^1H NMR (acetone-d_6) δ 7.68 (d, *J*=8.4 Hz, 2H), 7.49 (AA'BB', *J*=9.2 Hz, 4H), 6.98 (d, *J*=9.1 Hz, 2H), 4.23 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 3.19 (t, *J*=6.2 Hz, 2H), 2.62 (s, 3H), 1.64 (t, *J*=6.6 Hz, 2H), 1.19 (t, *J*=6.5 Hz, 2H) ppm.

Example 170

6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt

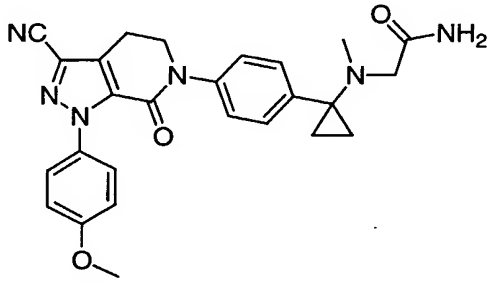


Following a procedure analogous to that used in Example 67 but using the product of Example 156 as the starting material, the title compound was prepared. HRMS $C_{25}H_{26}O_2N_5$

$(M+H)^+$ 428.2104 calcd for 428.2087. ^1H NMR (acetone-d_6) δ 7.70 (d, J=8.4 Hz, 2H), 7.55 (AA'BB', J=9.2 Hz, 4H), 7.00 (d, J=9.1 Hz, 2H), 4.26 (t, J=6.6 Hz, 2H), 3.83 (s, 3H), 3.22 (t, J=6.2 Hz, 2H), 2.79 (s, 6H), 1.70 (t, J=6.1 Hz, 2H), 1.17 (t, J=6.1 Hz, 2H) ppm.

Example 171

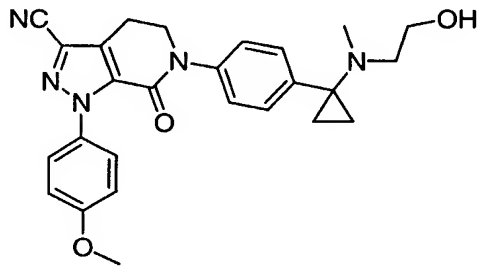
2-[(1-{4-[3-Cyano-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-methylamino]acetamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 162 but using the product of Example 169 as the starting material, the title compound was prepared. The product was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA) and lyophilized to dryness. LC/MS (ESI) 471.6 (M+H), t_R=2.14 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 172

6-(4-{1-[(2-Hydroxyethyl)methylamino]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt

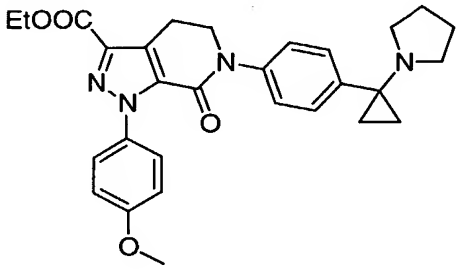


Following a procedure analogous to that used in Example 162 but using the product of Example 169 and 2-bromoethanol as

the starting materials, the title compound was prepared. The product was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA) and lyophilized to dryness. HRMS $C_{26}H_{28}N_5O_3$ $(M+H)^+$ 458.2196 calcd for 458.2193. ^1H NMR (CD_3OD) δ 7.68 (m, 2H), 7.46 (m, 4H), 6.98 (m, 2H), 4.17 (t, *J*=6.6 Hz, 2H), 3.82 (m, 5H), 3.29 (m, 2H), 3.17 (m, 2H), 2.92 (m, 3H), 1.61 (m, 2H), 1.34 (m, 2H) ppm. ^{19}F NMR (CD_3OD) δ -77.56 ppm.

Example 173

1-(4-Methoxyphenyl)-7-oxo-6-[4-(1-pyrrolidin-1-yl-cyclopropyl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid ethyl ester, trifluoroacetic acid salt

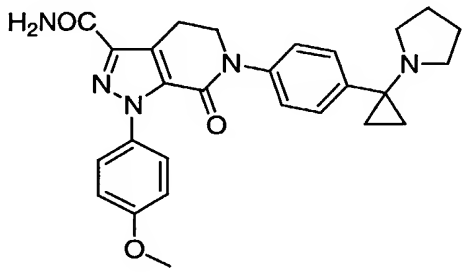


6-[4-(1-Amino-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (95 mg, 0.21 mmol), 1,3-dibromo-propane (0.03 mL, excess), and K_2CO_3 (100 mg, excess) were heated in DMF at 80°C for 24 h. EtOAc was added. The mixture was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by FCC (Silica gel, EtOAc, then 15% MeOH in EtOAc) to yield the title compound (89 mg, yield: 83.5%). HRMS $C_{29}H_{33}O_4N_4$ $(M+H)^+$ 501.2489 calcd for 501.2503. ^1H NMR ($CDCl_3$) δ 7.47 (d, *J*=8.8 Hz, 2H), 7.27 (AA'BB', *J*=8.8 Hz, 4H), 6.90 (d, *J*=8.9 Hz, 2H), 4.45 (q, *J*=7.1 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.80 (s, 3H), 3.31 (t, *J*=6.6 Hz, 2H),

2.52 (m, 4H), 1.61 (m, 4H), 1.43 (t, *J*=7.1 Hz, 2H), 0.97 (m, 2H), 0.77 (m, 2H) ppm.

Example 174

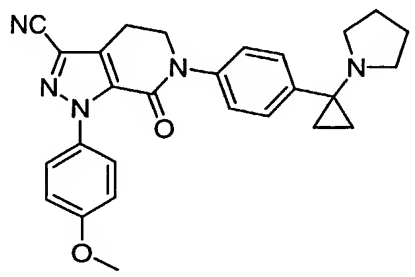
1-(4-Methoxyphenyl)-7-oxo-6-[4-(1-pyrrolidin-1-yl-cyclopropyl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67 but using the product of Example 173 as the starting material, the title compound was prepared. The product was purified by flash chromatography (silica gel, EtOAc, then 15% MeOH in EtOAc). LC/MS(ESI$^+$) 472.6 $(M+H)^+$, t_R=2.02 min (10-90% CH_3CN in H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ 7.39 (d, *J*=8.8 Hz, 2H), 7.21 (AA'BB', *J*=8.8 Hz), 6.86 (d, *J*=9.1 Hz, 2H), 4.04 (t, *J*=6.9 Hz, 2H), 3.74 (s, 3H), 3.30 (t, *J*=6.6 Hz, 2H), 2.47 (m, 4H), 1.54 (m, 4H), 0.93 (m, 2H), 0.71 (m, 2H) ppm.

Example 175

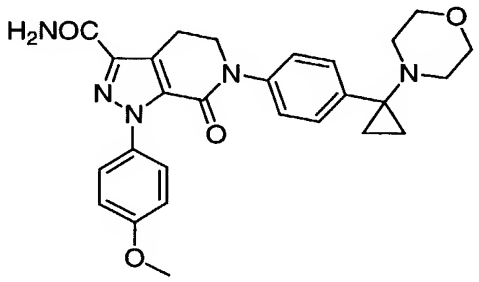
1-(4-Methoxyphenyl)-7-oxo-6-[4-(1-pyrrolidin-1-yl-cyclopropyl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74 but using the product of Example 174 as the starting material, the title compound was prepared. The product was purified by flash chromatography (silica gel, EtOAc, then 15% MeOH in EtOAc). LC/MS(ESI$^+$) 454.6 $(M+H)^+$, t_R=2.27 min (10-90% CH_3CN in H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ 7.39 (d, *J*=8.8 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 7.20 (d, *J*=8.5 Hz), 6.86 (d, *J*=9.2 Hz, 2H), 4.09 (t, *J*=6.6 Hz, 2H), 3.75 (s, 3H), 3.10 (t, *J*=6.6 Hz, 2H), 2.63 (m, 4H), 1.62 (m, 4H), 1.17 (m, 2H), 0.78 (m, 2H) ppm.

Example 176

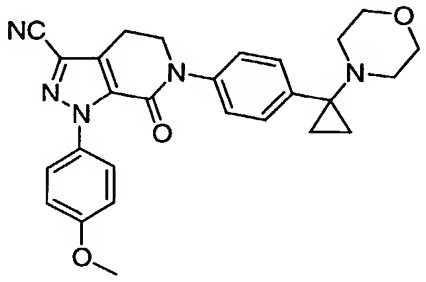
1-(4-Methoxyphenyl)-6-[4-(1-morpholin-4-yl-cyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



The product of Example 153 (45 mg, 0.108 mmol) and 1-bromo-2-(2-bromo-ethoxy)-ethane (0.25 mL), Et_3N (0.25 mL) were heated in DMF (1 mL) at 65°C for 3h under N_2. The mixture was evaporated, and the residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O with 0.5% TFA), and lyophilized to dryness. LC/MS(ESI$^+$) 488.6 $(M+H)^+$, t_R=1.97 min (10-90% CH_3CN in H_2O in a 4-min run). ^1H NMR (acetone-d_6) δ 7.51 (d, *J*=9.2 Hz, 2H), 7.49 (m, 4H), 6.97 (d, *J*=8.8 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 3.27 (m, 4H), 3.29 (t, *J*=6.6 Hz, 2H), 2.63 (m, 4H), 1.08 (m, 2H), 0.83 (m, 2H) ppm.

Example 177

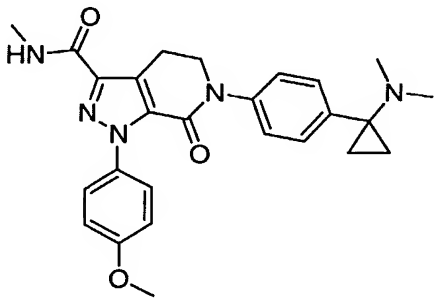
1-(4-Methoxyphenyl)-6-[4-(1-morpholin-4-yl-cyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 175 but using the product of Example 168 as the starting material, the title compound was prepared. The product was purified by flash chromatography (silica gel, EtOAc, then 10% MeOH in EtOAc). LC/MS(ESI$^+$) 470.6 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=9.2 Hz, 2H), 7.26 (m, 4H), 6.93 (d, *J*=9.2 Hz, 2H), 4.16 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.75 (m, 2H), 3.65 (m, 4H), 3.50 (t, *J*=6.3, 2H), 3.18 (t, *J*=6.6 Hz, 2H), 0.94 (m, 2H), 0.79 (m, 2H) ppm.

Example 178

6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid methylamide, trifluoroacetic acid salt

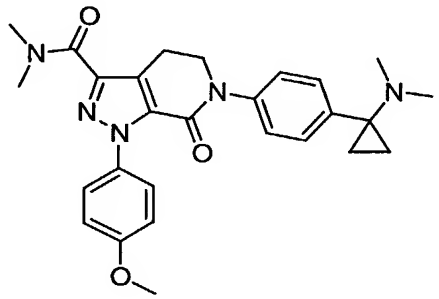


The product was purified by flash chromatography (silica gel, EtOAc, then 10% MeOH in EtOAc. HRMS $C_{26}H_{30}N_5O_3$ $(M+H)^+$

460.2319 calcd for 460.2349. ^{1}H NMR (acetone-d_6) δ 7.49 (d, J=9.1 Hz, 2H), 7.30 (m, 4H), 6.95 (d, J=8.8 Hz, 2H), 4.11 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.28 (t, J=6.6 Hz, 2H), 2.90 (d, J=4.7 Hz 3H), 2.15 (s, 6H), 0.83 (m, 2H), 0.73 (m, 2H) ppm.

Example 179

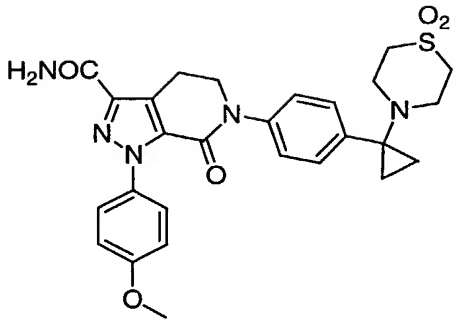
6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid dimethylamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 166, the title compound was prepared. The product was purified by flash chromatography (silica gel, EtOAc, then 10% MeOH in EtOAc). LC/MS(ESI$^+$) 474.6 $(M+H)^+$, t_R=6.08 min (10-90% CH_3CN in H_2O in a 4-min run). ^{1}H NMR (acetone-d_6) δ 7.50 (d, J=8.8 Hz, 2H), 7.32 (m, 4H), 6.95 (d, J=9.1 Hz, 2H), 4.10 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 3.18 (t, J=6.6 Hz, 2H), 3.04 (s, 3H), 2.19 (s, 6H), 0.87 (m, 2H), 0.75 (m, 2H) ppm.

Example 180

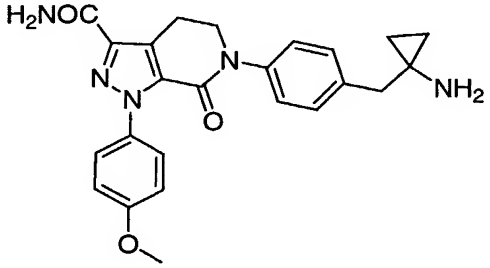
6-{4-[1-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



The product from Example 153 (90 mg, 0.22 mmol) was stirred in MeOH (1 mL) in a Pyrex® tube. Vinyl sulfone (0.1 mL) was added followed by the addition of Et_3N (0.2 mL). The tube was capped. The mixture was stirred at rt for 1h, and heated at 40-50°C for 1.5 h. After cooling, the solvents were evaporated. The residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O) and lyophilized to afford the desired product. LC/MS ESI 536.4 (M+H), t_R=2.49 (10-90% CH_3CN in H_2O in a 4-min run).

Example 181

6-[4-(1-Aminocyclopropylmethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-*1H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Part A. 4-Iodophenylacetonitrile (0.90 g, 3.70 mmol) was stirred in Et_2O (7 mL) at rt under N_2, $Ti(O\text{-}iPr)_4$ (1.20 ml, 1.1 eq) was added followed by dropwise addition of EtMgBr (2.0 M in Et_2O, 2.5 mL, 2.0 eq) at rt. The reaction mixture was stirred at rt for 0.5 h. $BF_3 \cdot Et_2O$ (0.94 ml, 2.0 eq) was added dropwise within 2 mins. The mixture was stirred at rt for 20 min. LC/MS showed one peak corresponding to the desired product. 1N NaOH (ca. 3 mL)

was added. It was extracted with Et_2O (2 x), washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to dryness to give 1-(4-iodo-benzyl)-cyclopropylamine (0.60 g, yield: 60%). LC/MS (ESI^+) 274.2 (M+H), t_R=1.61 min (10-90% CH_3CN in H_2O in a 4-min run).

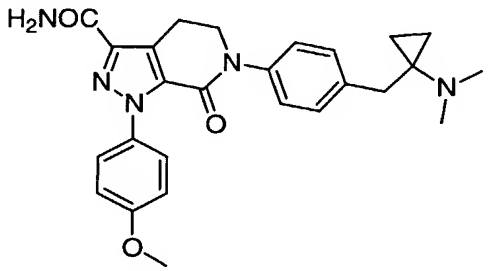
Part B. The product from Part A (0.60 g, 2.2 mmol) was stirred in CH_2Cl_2 (8 mL) at rt under N_2. $(Boc)_2O$ (0.57 g, 1.2 eq) was added followed by the addition of DIEA (0.61 mL, 1.5 eq). The mixture was stirred at rt for 3h. H_2O was added, the mixture was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, and concentrated to dryness to yield [1-(4-iodo-benzyl)-cyclopropyl]-carbamic acid *tert*-butyl ester (0.61 g, 75%). LC/MS (ESI^+) 318.0 (M-(*t*-Bu)+H), t_R=2.84 min (10-90% CH_3CN in H_2O in a 4-min run).

Part C. The product of Part B (0.18 g, 0.48 mmol) and 1-(4-mthoxy-phenyl)-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.15 g, 0.47 mmol) were stirred in DMSO (1.5 mL) under N_2. K_2CO_3 (0.13 g, 1.0 mmol, 2.1 eq) was added, followed by the addition of CuI (0.050 g, 0.26 mmol) and 1,10-phenanthroline (0.048 g, 0.26 mmol). The mixture was heated at 120°C for 3h. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2:EtOAc=1:1, then EtOAc) to give 6-[4-(1-tert-butoxycarbonylamino-cyclopropylmethyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.11 g, yield: 45%). LC/MS (ESI^+) 505.2 (M+H-t-Bu), t_R=2.75 min (35-98% CH_3CN in H_2O in a 6-min run).

Part D. The product from Part C (90 mg, 0.16 mmol) was stirred in saturated NH_3 in ethylene glycol at 80°C in a Pyrex® tube for 4h. The cooled mixture was diluted with H_2O, and extracted with EtOAc (2x). The organics were rinsed with H_2O and brine, dried over MgSO4, filtered, and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (5 mL), and TFA (3 mL) was added. The mixture was stirred at rt for 20 min. The solvent was evaporated, and the residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O) to afford pure title compound (45 mg, yield: 65.2%). ^1H NMR ($CDCl_3$) δ 7.47 (d, *J*=8.8 Hz, 2H), 7.21 (AA'BB', *J*=8.4 Hz, 4H), 6.93 (d, *J*=9.2 Hz, 2H), 4.10 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.37 (t, *J*=6.6 Hz, 2H), 2.82 (s, br, 2H), 0.75 (s, 4H) ppm. LC/MS (ESI^+) 432.6 (M+H), t_R=0.36 min (35-98% CH_3CN in H_2O in a 6-min run).

Example 182

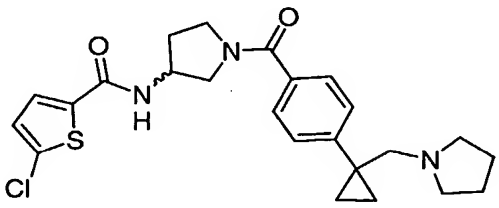
6-[4-(1-Dimethylaminocyclopropylmethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide, trifluoroacetic acid salt



Following the same procedure as shown in Example 155, the title compound was prepared. LC/MS(ESI^+) 460.6 $(M+H)^+$, t_R=2.14 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 183

5-Chloro-thiophene-2-carboxylic acid {1-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide, trifluoroacetic acid salt



Part A. 1-(4-Chlorocarbonyl-phenyl)-cyclopropanecarboxylic acid methyl ester (0.78 g, 3.28 mmol), pyrrolidin-3-yl-carbamic acid tert-butyl ester (0.60 g, 3.22 mmol) and DIEA (1.18 mL, 6.44 mmol) were stirred in CH_2Cl_2 (10 mL) at rt under N_2 overnight. H_2O was added. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, dried in vacuo. The residue was dissolved in MeOH (20 mL) and 1N NaOH (10 mL) was added. The reaction was heated at 50°C for 2.5h. The solvents were evaporated. The residue was extracted with Et_2O, the H_2O layer was acidified with citric acid, and extracted with Et_2O (2x), washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield 1-[4-(3-tert-butoxycarbonylamino-pyrrolidine-1-carbonyl)-phenyl]-cyclopropanecarboxylic acid methyl ester (1.08 g, yield: 83.0%).

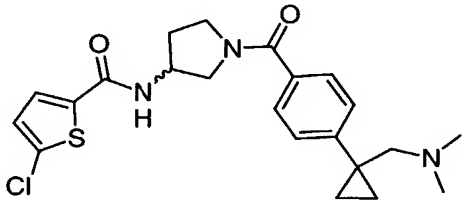
Part B. The product from Part A was treated with an analogous sequence as used in Part E and Part F of Example 1 but using pyrrolidine as the starting material and {1-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester was obtained.

Part C. The product from Part B was stirred in CH_2Cl_2 (20 mL) and TFA (10 mL) at rt for 1h. The solvents were evaporated to dryness. Part of the amine (ca. 20 mg) was

dissolved in DMF (0.5 mL). 5-Chloro-thiophenecarbocyclic acid (10 mg) was added followed by the addition of HATU (30 mg) and DIEA (0.03 mL). The reaction was stirred at rt overnight. It was purified via preparative LC/MS (5-98% CH_3CN in H_2O) to afford the desired title compound (12.1 mg, yield: 43.5 %). LC/MS(ESI$^+$) 458.6 (M+H), t_R=2.42 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 184

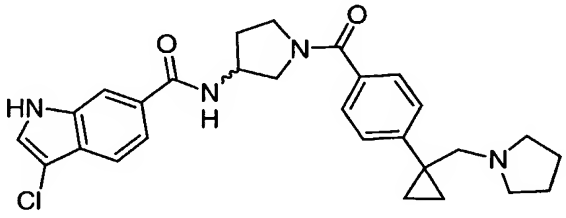
5-Chloro-thiophene-2-carboxylic acid {1-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 183, the title compound was prepared. LC/MS(ESI$^+$) 405.2 (M+H), t_R=2.61 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 185

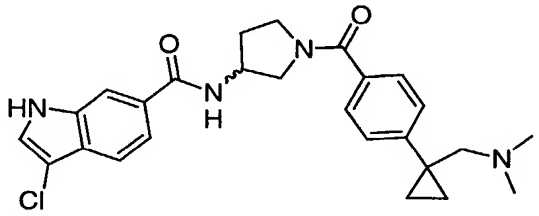
3-Chloro-1H-indole-6-carboxylic acid {1-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 183, the title compound was prepared. LC/MS (ESI$^+$) 491.4 (M+H).

Example 186

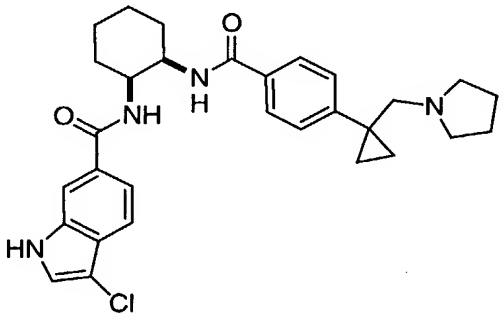
3-Chloro-1H-indole-6-carboxylic acid {1-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 183, the title compound was prepared. LC/MS (ESI$^+$) 465.4 (M+H).

Example 187

3-Chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide, trifluoroacetic acid salt



Part A. 1-(4-Chlorocarbonyl-phenyl)-cyclopropanecarboxylic acid methyl ester (0.66 g, 2.77 mmol) was stirred in CH_2Cl_2 (10 mL) at rt under N_2. 1,2-Cis-diamino-cyclohexane (0.66 mL, 2.0 eq) was added as one portion. The mixture was stirred for 10 min. Diluted HCl was added. The mixture was extracted with EtOAc (2x). The aqueous layer was basified with conc. NaOH, extracted with EtOAc (2x). The organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to afford 1-[4-(2-amino-cyclohexylcarbamoyl)-phenyl]-cyclopropanecarboxylic acid

methyl ester (0.35 g, yield: 39.8%). LC/MS (ESI^+) 317.4 (M+H).

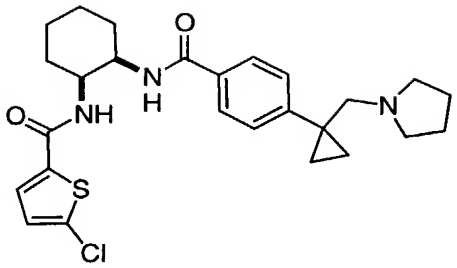
Part B. The product from Part A (0.15 g, 0.47 mmol) was stirred in DMF (1 mL) at rt. 3-Chloro-1*H*-indole-6-carboxylic acid (0.28 g, 1.36 mmol, 2.9 eq) and HATU (0.36 g, 0.95 mmol, 2.0 eq) were added followed by the addition of DIEA (0.30 mL, 1.71 mmol, 3.6 eq). The mixture was stirred at rt overnight. H_2O was added. The mixture was extracted with EtOAc (2x). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to dryness to afford 1-(4-{2-[(3-chloro-1H-indole-6-carbonyl)-amino]-cyclohexylcarbamoyl}-phenyl)-cyclopropanecarboxylic acid methyl ester (0.20 g, yield: 85.7%). LC/MS(ESI^+) 494.6 (M+H), t_R=3.22 min (35-95% CH_3CN in H_2O in a 6-min run).

Part C. The product from Part B was subjected to an analogous sequence as used in Part E and Part F of Example 1 but using pyrrolidine as the starting material to afford 3-chloro-6-{2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexylcarbamoyl}-indole-1-carboxylic acid ethyl ester. LC/MS(ESI^+) 591.6 (M+H).

Part D. The product from Part C was suspended in 4N HCl (20 mL) and heated at 50°C for 1h. The solvent was evaporated. The residue was purified by reverse phase HPLC (0-100% CH_3CN in H_2O) to afford the title compound (32 mg, yield: 33% for Part C and Part D). LC/MS(ESI^+) 519.4 (M+H), t_R=1.85 min (10-90% CH_3CN in H_2O in a 6-min run).

Example 188

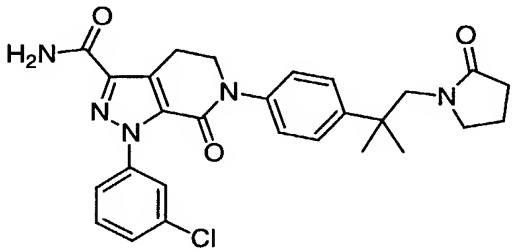
5-Chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 187, the title compound was prepared. LC/MS (ESI+) 466.4 (M+H).

Example 189

1-(3-Chloro-phenyl)-6-{4-[1,1-dimethyl-2-(2-oxo-pyrrolidin-1-yl)-ethyl]-phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Part A. To crude 2-(4-iodo-phenyl)-2-methyl-propionitrile (see Example 96) (1.5 g, 5.5 mmol) in THF (25 mL) at 0°C was added 1M Borane in THF (6 mL, 6 mmol) and the reaction was stirred 2h at rt. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, and dried (Na_2SO_4). The crude residue was treated with 1N HCl and extracted with diethyl ether. The aqueous layer was basified and extracted with ethyl acetate and dried to afford 0.38 g (25%) of a light brown oil. ^1H NMR ($CDCl_3$) δ 7.59 (d, *J*=8.4 Hz, 2H), 7.04 (d, *J*=8.4 Hz, 2H), 2.70 (s, 2H), 1.21 (s, 6H) ppm.

Part B. To the product from part A (1 g, 3.6 mmol) in CH_2Cl_2 (75 mL) in a separatory funnel were added cold 1N NaOH (25 mL) and 4-chlorobutylchloride (0.53 mL, 4.7 mmol). The reaction was shaken for 15 min, then separated and the

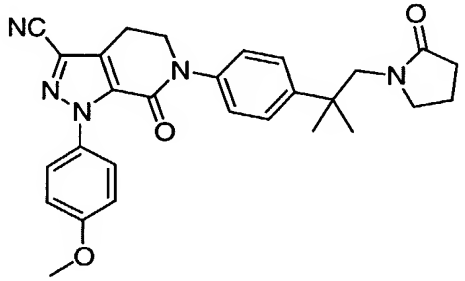
organic layer dried. To the crude amide in THF (30 mL) was added KOtBu (1.33 g, 10.9 mmol) at 0°C and the reaction was stirred 24h. The reaction was quenched with water, extracted with ethyl acetate, and dried to afford 1.1 g of crude lactam that was carried onto the next step.

Part C. The product from part B (0.26 g, 0.76 mmol), 1-(3-chloro-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.25 g, 0.76 mmol), and K_2CO_3(0.32 g,2.3 mmol) were combined and degassed DMSO(4 mL) followed by CuI (29 mg, 0.15 mmol) were then added. The reaction was heated to 130^{0}C for 5h. The reaction was cooled and partitioned between ethyl acetate and water and extracted with ethyl acetate and dried ($MgSO_4$). Chromatography on silica gel using 0-5%MeOH in CH_2Cl_2 afforded ester that was carried onto the next step.

Part D. The ester from part C was placed in 5%NH_3 in ethylene glycol (1.5 mL) and heated in a sealed tube at 80^{0}C for 2h. The reaction was cooled, poured into water, and filtered. Crystallization from CH_3CN/H_2O afforded 40 mg (10% for 2 steps) of the title compound. High Resolution Mass Spec for $C_{27}H_{29}ClN_5O_3(M+H)^+$ 506.1955.

Example 190

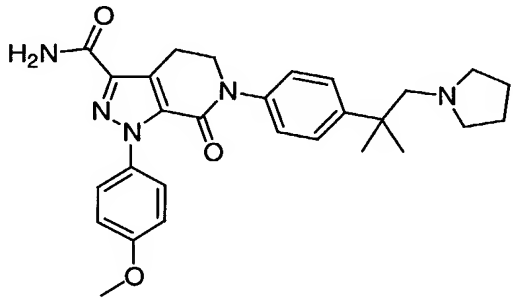
6-{4-[1,1-Dimethyl-2-(2-oxo-pyrrolidin-1-yl)-ethyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile



To 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile (0.149 g, 0.55 mmol), 1-[2-(4-iodo-phenyl)-2-methyl-propyl]-pyrrolidin-2-one (0.19 g, 0.55 mmol), and K_2CO_3 (0.23 g, 1.7 mmol) was added degassed DMSO (4 mL) followed by CuI (21 mg, 0.11 mmol). The mixture was heated to 130°C for 5h. The reaction was cooled, partitioned between ethyl acetate and water, extracted with ethyl acetate, and dried ($MgSO_4$). Chromatography on silica gel using 0-5%MeOH in CH_2Cl_2 followed by further purification by HPLC afforded the title compound (65 mg, 24%); HRMS for $C_{28}H_{30}N_5O_3$ $(M+H)^+$ 484.2363.

Example 191

1-(4-Methoxy-phenyl)-6-[4-(1-methyl-1-pyrrolidin-1-ylethyl)-phenyl]-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Part A. To pyrrolidine (1.2 g, 0.018 mol) in CH_2Cl_2 (50 mL) at 0°C was added 2M trimethylaluminum in heptane (9 mL, 0.018 mol) and the mixture was stirred 20 min. Ethyl-4-iodobenzoate (1 g, 3.6 mmol) was then added and the reaction was stirred 72h. The reaction was quenched with ice and 1N HCl, extracted with CH_2Cl_2, and dried ($MgSO_4$). To the crude amide was added THF (30 mL) and this solution was cooled to -20°C. To this solution TiCl4•2THF (1.2 g, 3.6 mmol) was added and stirred cold for 0.5h. A 3M diethyl ether solution of methylmagnesium bromide (7.2 mL, 21.7 mmol) was added and the reaction was stirred 24h at room temperature. Quenching with 30%NaOH, extracting with

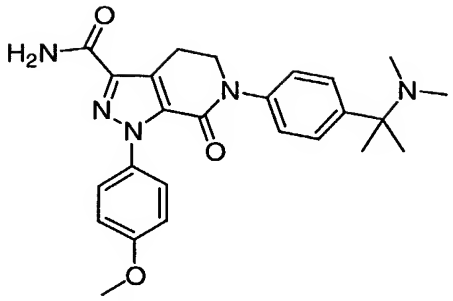
ethyl acetate, and drying (Na_2SO_4) followed by chromatography on silica gel using 0-5%MeOH in CH_2Cl_2 afforded 1-[1-(4-iodo-phenyl)-1-methyl-ethyl]-pyrrolidine (0.1 g, 8.8%); Mass spec $(M+H)^+$ 316.1.

Part B. To the product from part A (100 mg, 0.32 mmol), 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (119 mg, 0.38 mmol), and K_2CO_3 (0.11 g, 0.79 mmol) was added DMSO (4 mL) and the mixture was then degassed with N_2. CuI (12 mg, 0.063 mmol) was added. The reaction was heated to 130°C for 6h. The reaction was quenched with sat'd $NaHCO_3$, extracted with CH_2Cl_2, and dried ($MgSO_4$). Chromatography on silica gel using 0-5%MeOH (1%NH_3) in CH_2Cl_2 afforded 60 mg (37.7%) of ester; Mass Spec $(M+H)^+$ 503.5.

Part C. To the ester (60 mg, 0.12 mmol) was added 5% NH_3 in ethylene glycol (1 mL) and the reaction was heated 80°C in a sealed tube for 2h. A solid precipitate was collected after dilution with water and the filtrate was extracted with CH_2Cl_2. The product was purified by HPLC and freeze-dried to afford the title compound (45 mg, 64%); High Resolution Mass Spectrum for $C_{27}H_{32}N_5O_3$ $(M+H)^+$ 474.2516.

Example 192

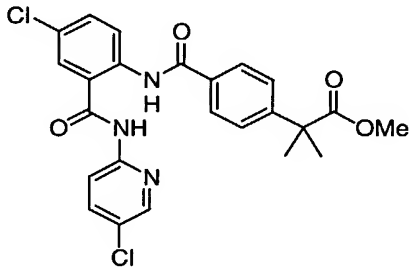
6-[4-(1-Dimethylamino-1-methyl-ethyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used in Example 191, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{25}H_{30}N_5O_3$ 448.2327.

Example 193

2{4-[4-Chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester



Step A. To a solution of 2-amino-4-chloropyridine (129.0 mg, 1.0 mmol) in anhydrous THF at -78°C was added KHMDS (4.0 ml, 0.5 M solution in toluene). The mixture was stirred at this temperature under N_2 for 30 min. and a solution of 5-chloro-isatoic anhydride (198.0 mg, 1.0 mmol) in THF was added to the above mixture. The resulted mixture was warmed to rt gradually and stirred for 10 hr. The reaction mixture was quenched with sat'd NH_4Cl solution, most of the solvent was evaporated and the residue was diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Removal of solvent and chromatography on silica gel (20% ethyl acetate in hexane) yielded the desired product 2-amino-5-chloro-N-(5-chloro-pyridin-2-yl)-benzamide as light brown solid. MS found: $(M+1)^+$=282.2.

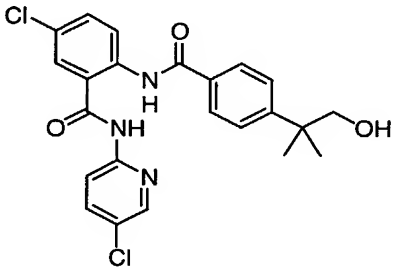
Step B. To a mixture of methyl phenylacetate (150.0 mg, 1.0 mmol) in THF at -78°C was added NaHMDS (2.2 ml, 2.2 mmol). After stirring at this temperature for 15 min, MeI (312.0 mg, 2.2 mmol) was added to the above mixture. The resulted mixture was stirred at -78°C for 3 hr and rt for 1 hr. The mixture was cooled to -78°C, quenched with sat'd NH_4Cl, diluted with EtOAc, washed with aq. $NaHCO_3$ and brine, and dried. Flash chromatography purification (10% EtOAc in hexane) gave 2-methyl-2-phenyl-propionic acid methyl ester as clear oil. MS found: $(M+1)^+$=179.1.

Step C. To a suspension of $AlCl_3$ (500.0 mg, 3.75 mmol) in CH_2Cl_2 at -10 °C was added dropwise oxalyl chloride (476.0 mg, 3.75 mmol) in CH_2Cl_2. The mixture was stirred at this temperature for 30 min. Then a solution of 2-methyl-2-phenyl-propionic acid methyl ester (178.0 mg, 1.0 mmol) in CH_2Cl_2 was added. The resulted mixture was stirred at -10 °C for 1 hr and rt overnight. The mixture was filtered through a pad of celite, the solvent and excess oxalyl chloride was removed under reduced pressure. The residue was dissolved in chlorobenzene and refluxed for 4 hr. Solvent was removed and the residue was dried to give 2-(4-chlorocarbonyl-phenyl)-2-methyl-propionic acid methyl ester.

Step D. To a solution of 2-(4-chlorocarbonyl-phenyl)-2-methyl-propionic acid methyl ester (240.0 mg, 1.0 mmol) in CH_2Cl_2 at 0 °C was added TEA (3.0 mmol) followed by addition of 2-amino-5-chloro-N-(5-chloro-pyridin-2-yl)-benzamide (281 mg, 1.0 mmol) and DMAP (cat. 10 mg). The resulted mixture was stirred at 0 °C for 1 hr and rt over night. Solvent was evaporated and HPLC purification gave 2{4-[4-Chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester as white solid. MS found: $(M+1)^+$=486.2.

Example 194

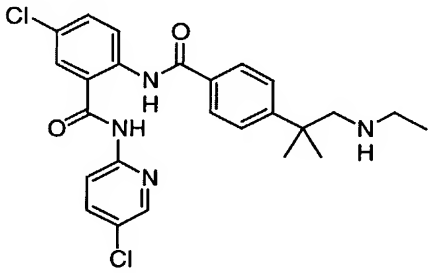
2{4-[4-Chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propyl alcohol



To a solution of 2{4-[4-Chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester (485.0 mg, 1mmol) in THF was added $LiBH_4$ (2.0 ml, 2.0 M solution in THF). The mixture was stirred at 60 °C over night. The reaction mixture was cooled, and quenched with sat'd NH_4Cl. HPLC purification gave 2{4-[4-Chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propyl alcohol as white solid. MS found: $(M+1)^+$=457.9.

Example 195

5-chloro-*N*-(5-chloropyridin-2-yl)-2-({4-[2-(ethylamino)-1,1-dimethylethyl]benzoyl}amino)benzamide

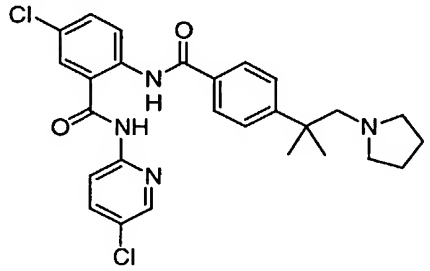


Step A. To a solution of the product obtained from Example 194 (457.0 mg, 1.0 mmol) in CH_2Cl_2 was added Dess-Martin reagent (636.0 mg, 1.5 mmol). The mixture was stirred at rt for 2.5 hr. The mixture was filtered and solvent was removed to give the desired aldehyde that was used for next step.

Step B. To a solution of the above aldehyde (46.0 mg, 0.1 mmol) in CH_2Cl_2 was added diethylamine (0.2 mmol) and $NaBH_3CN$ (10.0 mg). The mixture was stirred at rt over night. The reaction mixture was filtered and HPLC purification gave the desired product as white solid. MS found: $(M+1)^+$=485.0.

Example 196

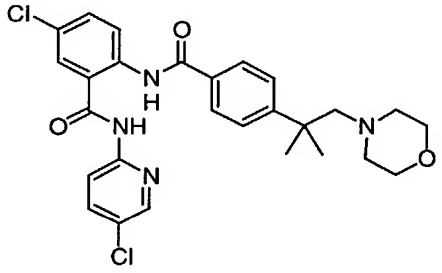
5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}benzamide



Following a procedure analogous to Example 195, the desired compound was obtained as white solid. MS found: $(M+1)^+$=511.3.

Example 197

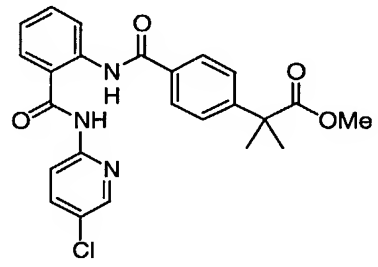
5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-morpholin-4-ylethyl)benzoyl]amino}benzamide



Following a procedure analogous to Example 195, the desired compound was obtained as white solid. MS found: $(M+1)^+$=527.3.

Example 198

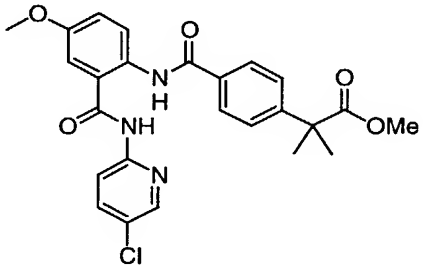
2-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester



Following a procedure analogous to Example 193, the desired compound was obtained as white solid. MS found: $(M+1)^+=452.1$.

Example 199

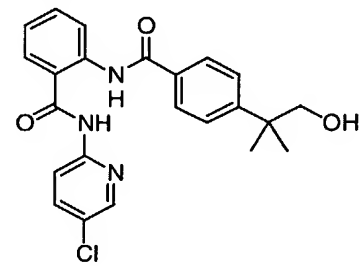
2-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-4-methoxy-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester



Following a procedure analogous to Example 193, the desired compound was obtained as white solid. MS found: $(M+1)^+=482.1$.

Example 200

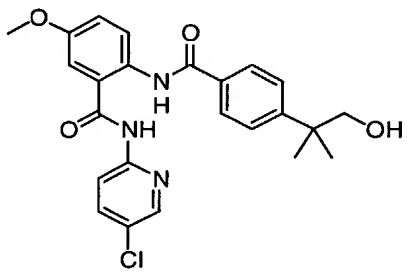
***N*-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzoyl]amino}benzamide**



Following a procedure analogous to Example 2, the desired compound was obtained as white solid. MS found: $(M+1)^+=424.1$.

Example 201

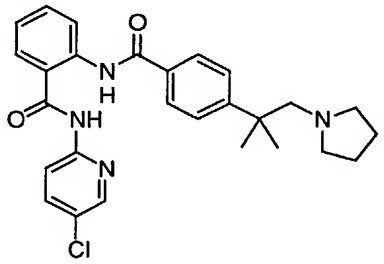
***N*-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzoyl]amino}-5-methoxybenzamide**



Following a procedure analogous to Example 194, the desired compound was obtained as white solid. MS found: $(M+1)^+=454.1$.

Example 202

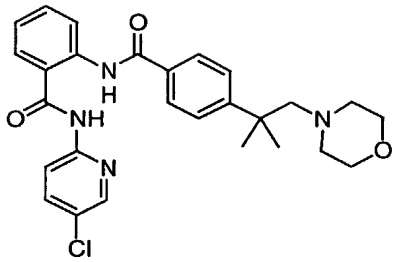
***N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}benzamide**



Following a procedure analogous to Example 195, the desired compound was obtained as white solid. MS found: $(M+1)^+=577.1$.

Example 203

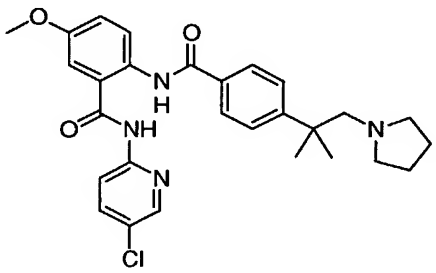
***N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-morpholin-4-ylethyl)benzoyl]amino}benzamide**



Following a procedure analogous to Example 195, the desired compound was obtained as white solid. MS found: $(M+1)^+=493.1$.

Example 204

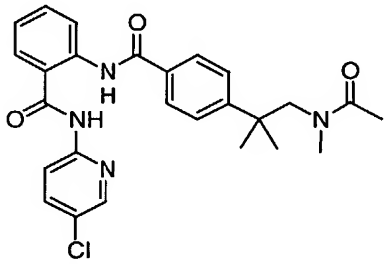
***N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}-5-methoxybenzamide**



Following a procedure analogous to Example 195, the desired compound was obtained as white solid. MS found: $(M+1)^+=507.1$.

Example 205

2-[(4-{2-[acetyl(methyl)amino]-1,1-dimethylethyl}benzoyl)amino]-*N*-(5-chloropyridin-2-yl)benzamide



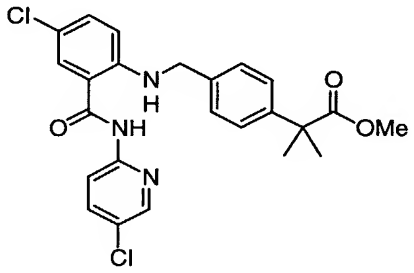
Step A. Following a procedure analogous to Example 195, the desired amine *N*-(5-chloropyridin-2-yl)-2-({4-[1,1-dimethyl-

2-(methylamino)ethyl]benzoyl}-amino)benzamide was obtained as white solid.

Step B. To a solution of the above amine (10.0 mg, 0.018 mmol) in CH_2Cl_2 at 0°C was added Ac_2O (10 µl) and TEA (50 µl). The mixture was stirred at 0°C for 4 hr. Solvent was removed and the residue was purified with reverse phase HPLC. MS found: $(M+1)^+$=479.2.

Example 206

2-(4-{[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylamino]methyl}-phenyl)-2-methyl-propionic acid methyl ester



Step A. The product obtained from Example 193, Step C (240.0 mg, 1.0 mmol) was treated with THF/H_2O (1:1, 10 ml). The mixture was stirred at 60°C for 2 hr. The reaction mixture was extracted with EtOAc, washed with 1N HCl, H_2O and brine. Reverse phase HPLC purification provided 4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoic acid as white solid. MS found: $(M+1)^+$=223.1.

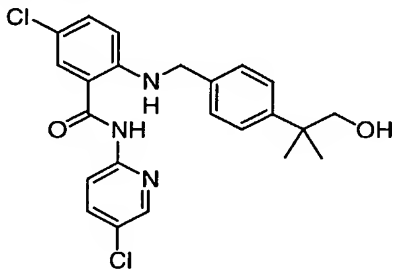
Step B. To a solution of the product obtained above (222.0 mg, 1.0 mmol) in THF was added BH3-THF (0.75 ml, 1.0 M solution in THF). The mixture was stirred at 65°C for 7 hr. Then the reaction mixture was cooled to rt and quenched with H_2O. After removal of solvent, the residue was purified with reverse phase to give 2-(4-hydroxymethyl-phenyl)-2-methyl-propionic acid methyl ester as clear oil. MS found: $(M+1)^+$=209.2.

Step C. To a solution of the product obtained above (83.0 mg, 0.399 mmol) in CH_2Cl_2 was added Dess-Martin reagent (203.0 mg, 0.48 mmol). The mixture was stirred at rt for 4 hr. The mixture was filtered, solvent was evaporated and the residue was dried to give the corresponding aldehyde, which was directly used in the next step.

Step D. A mixture of the product from above (66.0 mg, 0.32 mmol) and 2-amino-5-chloro-N-(5-chloro-pyridin-2-yl)-benzamide (90.0 mg, 0.32 mmol) in ethanol was refluxed under N_2 for 2 hr. After the mixture was cooled to room temperature, $NaBH_4$ (100.0 mg) was added, and the resulted mixture was stirred at rt over night. The reaction mixture was quenched with H_2O, and solvent was evaporated. The residue was purified with reverse phase HPLC to give desired product as white solid. MS found: $(M+1)^+$=472.0.

Example 207

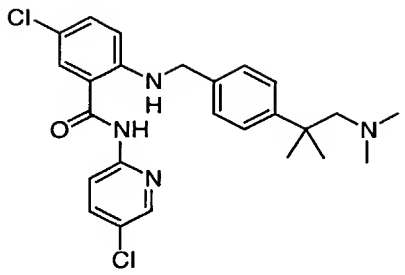
5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzyl]amino}benzamide



Following a procedure analogous to Example 194, the desired compound was obtained as white solid. MS found: $(M+1)^+$=444.1.

Example 208

5-Chloro-N-(5-chloro-pyridin-2-yl)-2-[4-(2-dimethylamino-1,1-dimethyl-ethyl)-benzylamino]-benzamide



Step A. To a solution of 2-methyl-2-phenylpropionic acid (5.0 g, 30.49 mmol) in CH_2Cl_2 at 0°C was added oxalyl chloride (4.0 ml, 45.7 mmol). The mixture was stirred at 0°C for 3 hr. Solvent was evaporated and the residue was dried.

The above residue was dissolved in CH_2Cl_2, and dimethylamine was purged for 20 min. or until saturated. The mixture was stirred rt for 1hr. The reaction mixture was washed with water, 1N HCl, sat'd $NaHCO_3$, and brine. Chromatography purification gave N,N-dimethyl-2-phenyl-isobutyramide as white solid. MS found: $(M+1)^+$=192.2.

Step B. Following a procedure analogous to Example 193, Step C, 4-(1-dimethylcarbamoyl-1-methyl-ethyl)-benzoyl chloride was obtained as colorless oil.

A solution of the product obtained above (2.45 g, 9.7 mmol) in MeOH at 0°C was added Et_3N (40 ml) and DMAP (20 mg). The resulted mixture was stirred at 0°C for 1 hr and rt over night. Then most of the solvent was removed, the residue was diluted with EtOAc. The resulted mixture was washed with 1N HCl, water and brine. Chromatography purification (30% EtOAc in hexane) provided 4-(1-dimethylcarbamoyl-1-methyl-ethyl)-benzoic acid methyl ester as white solid. MS found: $(M+1)^+$=250.1.

Step C. To a solution of the product obtained above (35.0 mg, 0.14 mmol) in THF at 0°C was added LAH (0.7 ml, 1.0 M

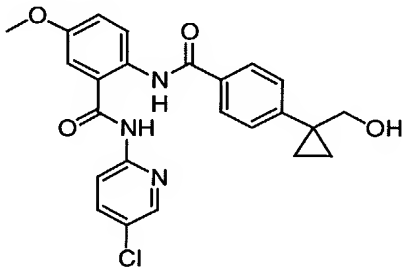
solution in THF). The mixture was stirred at 0°C for 1 hr and rt over night. Then the reaction mixture was quenched with sat'd potassium sodium tartrate solution. Solvent was evaporated and the residue was purified with reverse phase HPLC. The desired [4-(2-dimethylamino-1,1-dimehtyl-ethyl)-phenyl]-methanol was obtained as clear oil. MS found: $(M+1)^+$=208.2.

Step D. Following a procedure analogous to Example 195, Step A, the above alcohol was oxidized to 4-(2-dimethylamino-1,1-dimethyl-ethyl)-benzaldehyde. MS found: $(M+1)^+$=206.2.

Step E. Following a procedure analogous to Example 206, Step D, the desired compound was obtained as light yellow solid. MS found: $(M+1)^+$=471.1.

Example 209

***N*-(5-chloropyridin-2-yl)-2-({4-[1-(hydroxymethyl)cyclopropyl]benzoyl}amino)-5-methoxybenzamide**



Step A. Following a procedure analogous to Example 193, Step C, 1-phenyl-cyclopropanecarboxylic acid methyl ester was converted to the desired 1-(4-chlorocarbonyl)-cyclopropanecarboxylic acid methyl ester.

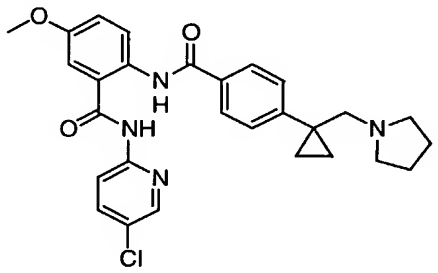
Step B. Following a procedure analogous to Example 193, Step D, the desired 1-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-4-methoxy-phenylcarbamoyl]-phenyl}-

cyclopropanecarboxylic acid methyl ester was obtained as white solid. MS found: $(M+1)^+$=480.1.

Step C. Following a procedure analogous to Example 194, the desired product was obtained as yellow solid. MS found: $(M+1)^+$=452.1.

Example 210

***N*-(5-chloropyridin-2-yl)-5-methoxy-2-({4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]benzoyl}amino)benzamide**

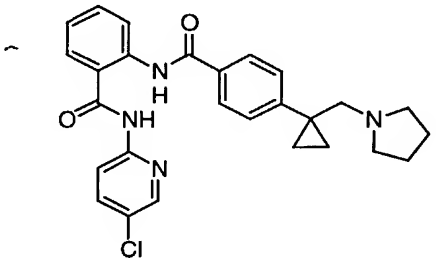


Step A. To a solution of the product obtained from Example 209 (20 mg, 0.044 mmol) in CH_2Cl_2 was added Dess-Martin reagent (28.0 mg, 0.066 mmol). The mixture was stirred at rt for 2.5 hr. Then the reaction mixture was filtered, the solvent was removed and the residue was dried to give the corresponding aldehyde.

Step B. To a solution of the aldehyde from above (15.0 mg, 0.033 mmol) in 1,2-dichloroethane at 0°C was added pyrrolidine (1.0 mL) and 2 drops of AcOH. The mixture was stirred at 0°C for 10 min, and $NaBH(OAc)_3$ (35 mg, 0.16 mmol) was added. The resulted mixture was warmed to rt slowly and stirred for 3 hr. After quenching with H_2O, the mixture was concentrated and the residue was purified with reverse phase HPLC to give the desired product as white solid. MS found: $(M+1)^+$=505.2.

Example 211

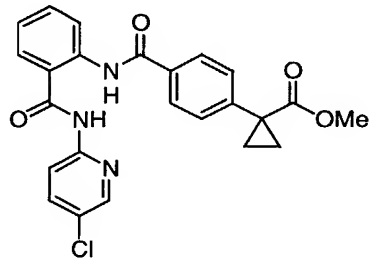
N-(5-chloropyridin-2-yl)-2-({4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]benzoyl}amino)benzamide



Following a procedure analogous to Example 210, the desired product was obtained as white solid. MS found: $(M+1)^+=475.2$.

Example 212

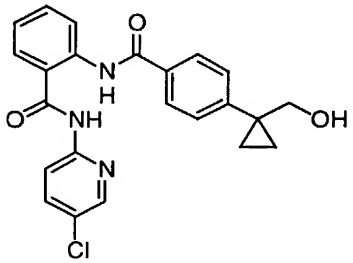
1-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-cyclopropanecarboxylic acid methyl ester



Following a procedure analogous to Example 209, Step A, the desired product was obtained as white solid. MS found: $(M+1)^+=450.1$.

Example 213

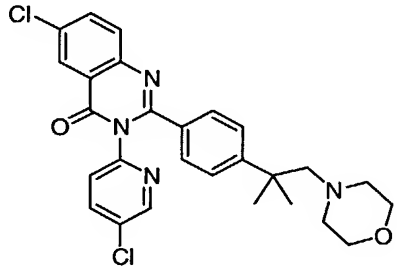
N-(5-chloropyridin-2-yl)-2-({4-[1-(hydroxymethyl)cyclopropyl]benzoyl}amino)benzamide



Following a procedure analogous to Example 209, the desired product was obtained as white solid. MS found: $(M+1)^+$=422.1.

Example 214

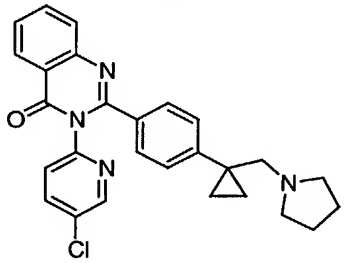
6-chloro-3-(5-chloropyridin-2-yl)-2-[4-(1,1-dimethyl-2-morpholin-4-ylethyl)phenyl]quinazolin-4(3*H*)-one



A solution of the product from Example 197 (15.0 mg, 0.028 mmol) in 5 ml of 4N HCl in dioxane and 0.5 mL of THF was refluxed for 6 hr. The mixture was cooled to rt and purified with reverse phase HPLC to give the desired product as white solid. MS found: $(M+1)^+$=509.1.

Example 215

3-(5-chloropyridin-2-yl)-2-{4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}quinazolin-4(3*H*)-one

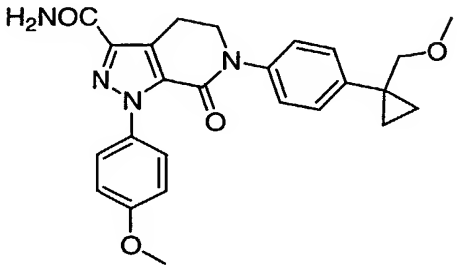


Following a procedure analogous to Example 214, the desired product was obtained as a white solid. MS found: $(M+1)^+$=457.1.

Example 216

6-[4-(1-Methoxymethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazo

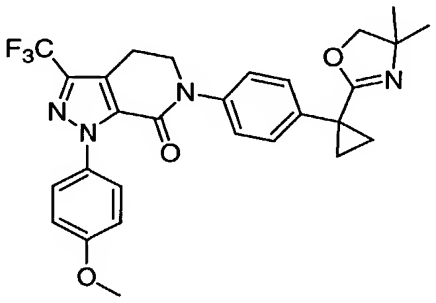
lo[3,4-c]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used in Example 140, the title compound was prepared. LC/MS (ESI^+) 447.4 (M+H).

Example 217

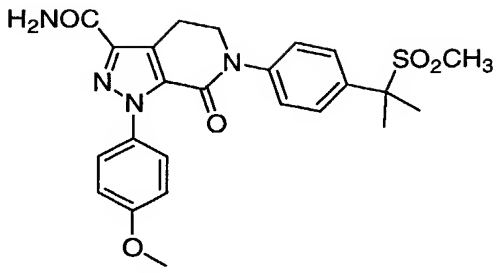
6-{4-[1-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



Following a procedure analogous to that used in Example 140, the title compound was prepared. LC/MS (ESI^+) 525.6 (M+H), t_R=2.05 min (10%-90% AcCN/H_2O in a 4-min run).

Example 218

6-[4-(1-Methanesulfonyl-1-methyl-ethyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Part A. To 4-iodobenzyl bromide (5 g, 0.018 mol) in DMF (15 mL) cooled to 0°C was added sodium thiomethoxide (1.2 g, 0.017 mol). The reaction was stirred 18 h at room temperature. The reaction was partitioned between ethyl acetate and water. The aqueous layer was extracted, washed with water and brine, and dried (Na_2SO_4). The crude oil obtained was carried onto the next step.

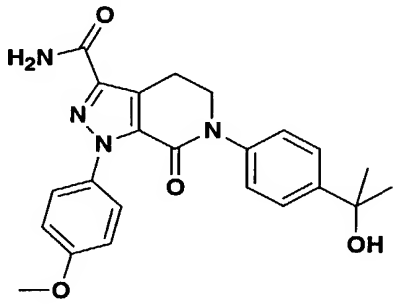
Part B. The product of Part A (0.6 g, 2.3 mmol), 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.6 g, 1.9 mmol), K_2CO_3 (0.66 g, 4.7 mmol), and dimethylsulfoxide (5 mL) were combined and degassed with N_2. Copper(I) iodide (72 mg, 0.38 mmol) was added and the reaction was heated to 130°C for 5 h. The reaction was quenched with sat'd $NaHCO_3$, extracted with CH_2Cl_2, and dried ($MgSO_4$). Purification by chromatography using 1:1 hexanes/ethyl acetate afforded 0.55 g (64%) of product; High Resolution Mass Spec for $C_{24}H_{26}N_3O_4S$ $(M+H)^+$ 452.1652.

Part C. To the product of Part B (0.27 g, 0.59 mmol) in CH_2Cl_2 (15 mL) at 0°C was added 3-chloroperbenzoic acid (0.4 g) and the reaction was stirred for 72 h. The reaction was washed with sat'd $NaHCO_3$, and dried ($MgSO_4$) to afford impure product. The product was dissolved in ethyl acetate washed twice with sat'd $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to afford 0.3 g of a yellow foam; High Resolution Mass Spec for $C_{24}H_{26}N_3O_6S$ $(M+H)^+$ 484.1541.

Part D. To the product of Part C (0.24 g, 4.9 mmol) in DMF (5 mL) at 0°C was added NaH (60 mg,14.7 mmol) and iodomethane (0.09 mL, 14.7 mmol). The reaction was stirred 24 h, then quenched with water, extracted with ethyl acetate, and dried($MgSO_4$). To the crude ester 5% NH_3 in ethylene glycol (2 mL) was added and the reaction was heated in a sealed tube at 80°C for 2h. The reaction was quenched with water and the resulting precipitate collected. Purification of the solid by HPLC and freeze-drying afforded 15 mg (6%) of the title compound; High Resolution Mass Spec for $C_{24}H_{27}N_4O_5S$ $(M+H)^+$ 483.1694.

Example 219

6-[4-(1-Hydroxy-1-methyl-ethyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Part A. To ethyl 4-iodobenzoate (1 g, 3.6 mmol) in THF (20 mL) at 0°C was added 3M methyl magnesium bromide (3 mL, 9 mmol). The reaction was stirred for 72h, quenched with 1N HCl, extracted with ethyl acetate, and dried (Na_2SO_4) to afford 0.94 g (100%) of the alcohol; ^1H NMR ($CDCl_3$) δ 7.67 (d, *J*=8.8Hz,2H), 7.25 (d, *J*=8.8Hz,2H), 1.56 (s,6H) ppm.

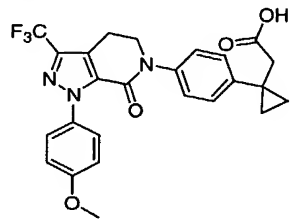
Part B. The product of Part A (0.9 g, 3.4 mmol), 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (1 g, 3.4 mmol), K_2CO_3 (1.2 g, 8.5 mmol), and DMSO (10 mL) were combined and

degassed with N_2. Copper(I) iodide (130 mg,0.68 mmol) was added, and the reaction was heated to 130°C for 18h. The reaction was quenched with sat'd $NaHCO_3$, extracted with CH_2Cl_2, and dried ($MgSO_4$). Purification by chromatography using 1:1 hexanes/ethyl acetate afforded an impure product; Mass Spec $(M+H)^+$ 450.6.

Part C. To the impure product of Part B (0.8 g) was added 5% NH_3 in ethylene glycol (8 mL), and the reaction was heated in a sealed tube at 80°C for 2h. The reaction was quenched with water and extracted with ethyl acetate. Purification of the solid by HPLC and freeze-drying afforded 120 mg of the title compound; High Resolution Mass Spec for $C_{23}H_{25}N_4O_4$ $(M+H)^+$ 421.1862.

Example 220

(1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-acetic acid



Part A. 1-(4-Iodophenyl)-cyclopropanecarbonyl chloride (1.74 g, 5.69 mmol) was stirred in CH_3CN and THF (1:1 v/v, 20 mL total) at 0°C under N_2. $TMSCHN_2$ (2M in hexanes, 4.3 mL, 1.5 eq) was added dropwise. The mixture was stirred at room temperature for 4 h. It was evaporated; sat'd $NaHCO_3$ was added. It was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was stirred in *t*-BuOH (20 mL) at gentle reflux. A mixture of silver benzoate (0.7 g, 3.07 mmol) and Et_3N (5 mL) was added over 1 min.

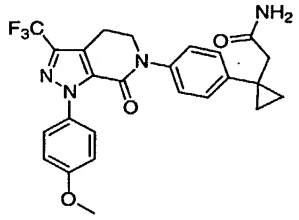
The reaction was stirred at reflux for 1 h, and the hot mixture was filtered through Celite®. H_2O was added to the filtrate; the mixture was extracted with EtOAc (3x). The organics were washed with sat'd $NaHCO_3$, H_2O, 1M HCl, sat'd $NaHCO_3$, H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, hexanes:CH_2Cl_2 = 1:0 to 1:1 to 0:1 then 10% EtOAc in CH_2Cl_2) to give [1-(4-iodo-phenyl)-cyclopropyl]-acetic acid *tert*-butyl ester (0.69 g, yield: 35%). ^1H NMR ($CDCl_3$): δ 7.49 (d, *J*=8.8 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 2H), 2.39 (s, 2H), 1.27 (s, 9H), 0.81 (s, 4H) ppm. LC/MS(ESI$^+$) 359.4 (M+H).

Part B. The product from Part A (0.34 g, 0.95 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.31 g, 0.99 mmol) were stirred in DMSO (1 mL) in a Pyrex® tube under N_2. K_2CO_3 (0.33 g, 2.39 mmol) was added, followed by the addition of CuI (95 mg, 0.50 mmol) and 1,10-phenanthroline (90 mg, 0.50 mmol). The mixture was stirred at 120°C for 3 h. LC/MS showed 70% conversion. The cooled mixture was extracted with EtOAc (3x), washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, hexanes:CH_2Cl_2=1:0 to 1:1 to 0:1, then EtOAc:CH_2Cl_2=1:10 to 1:2) to give (1-{4-[1-(4-methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-acetic acid *tert*-butyl ester (0.35 g, yield: 67%). ^1H NMR ($CDCl_3$) δ 7.48 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.16 (t, *J*=6.6 Hz, 2H), 2.51 (s, 2H), 1.39 (s, 9H), 0.91 (s, 4H) ppm. LC/MS(ESI) 542.4 (M+H).

Part C. The product from Part B (300 mg, 0.55 mmol) was stirred in CH_2CH_2 (10 mL) and TFA (5 mL) at rt for 4 h. It was purified by FCC (silica gel, EtOAc, then 10% MeOH in CH_2Cl_2) to give the desired title compound (235 mg, yield: 87.4%). ^1H NMR ($CDCl_3$) δ 7.43 (d, *J*=8.8 Hz, 2H), 7.34 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 5.23 (s, 2H), 4.11 (t, *J*=6.8 Hz, 2H), 3.81 (s, 3H), 3.16 (t, *J*=6.6 Hz, 2H), 2.63 (s, 2H), 0.95 (m, 2H), 0.91 (m, 2H) ppm. LC/MS(ESI) 486.6 (M+H). HRMS (ESI), $C_{25}H_{23}N_3O_4F_3$, calcd for 486.1641, found 486.1649.

Example 221

2-(1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-acetamide

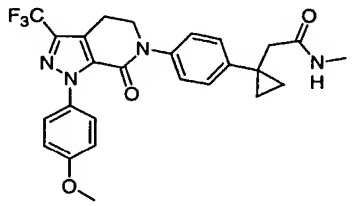


The acid chloride product from Example 210 (12.5 mg, 0.03 mmol) was stirred in THF (0.5 mL) at rt. Concentrated aqueous NH_3 (0.5 mL) was added. The mixture was stirred at rt for 4 h. LC/MS showed completion of the reaction. The mixture was purified by RP HPLC to give the title compound (9.0 mg, yield: 71.5%). ^1H NMR ($CDCl_3$) δ 7.38 (d, *J*=8.8 Hz, 2H), 7.26 (m, 4H), 6.84 (d, *J*=8.8Hz, 2H), 5.23 (s, 2H), 4.04 (m, 2H), 3.74 (s, 3H), 3.08 (m, 2H), 2.48 (s, 2H), 0.91 (m, 4H) ppm. LC/MS(ESI) 485.6 (M+H).

Using the same procedure as that described for Example 221, Examples 222-224 were prepared.

Example 222

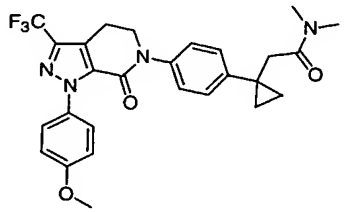
2-(1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-N-methyl-acetamide



^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.26 (m, 4H), 6.92 (d, *J*=8.8Hz, 2H), 4.11 (t, *J*=6.3 Hz, 2H), 3.81 (s, 3H), 3.15 (t, *J*=6.3 Hz, 2H), 2.69 (m, 3H), 2.52 (s, 2H), 1.78 (m, 4H), 0.95 (m, 4H) ppm. HRMS (ESI) calcd. 499.1958; found 499.1970 for $C_{26}H_{26}F_3N_4O_3$ (M+H). LC/MS (10-90%CH_3CN in H_2O in a 4-min run, t_R=2.30 min), 499.6(M+H).

Example 223

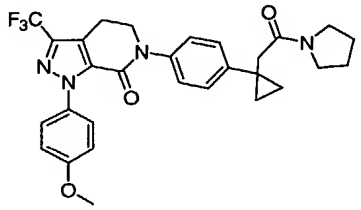
2-(1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropyl)-N,N-dimethyl-acetamide



^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.38 (d, *J*=8.5 Hz, 2H), 7.19 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8Hz, 2H), 4.10 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.13 (t, J=6.6 Hz, 2H), 2.86 (s, 3H), 2.76 (s, 3), 2.64 (s, 3H), 0.89 (m, 4H) ppm. HRMS (ESI), calcd. 513.2114; found 513.2113 for $C_{27}H_{28}F_3N_4O_3$ (M+H). LC/MS (10-90%CH_3CN in H_2O in a 4-min run, t_R=2.46 min), 513.6 (M+H).

Example 224

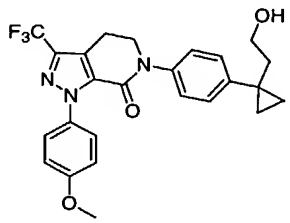
1-(4-Methoxy-phenyl)-6-{4-[1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-cyclopropyl]-phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.18 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8Hz, 2H), 4.10 (t, *J*=6.6Hz, 2H), 3.81 (s, 3H), 3.38 (t, *J*=6.4 Hz, 2H), 3.13 (m, 4H), 2.56 (s, 2H), 1.78 (m, 4H), 0.92 (m, 2H), 0.88 (m, 2H) ppm. HRMS(ESI) calcd. 539.2271; found 539.2214 for $C_{28}H_{30}F_3N_3O_3$ (M+H). LC/MS (ESI) (10-90%CH_3CN in H_2O in a 4-min run, t_R= 2.52 min) 539.6 (M+H).

Example 225

6-{4-[1-(2-Hydroxy-ethyl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one

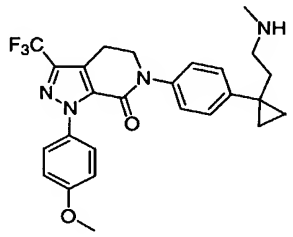


Using the similar sequence for the preparation of Part E in Example 1 but using the product of Example 220 as the starting material, the title compound was prepared. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.31 (d, *J*=8.8 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 6.92 (d, *J*=9.2 Hz, 2H), 5.23 (s, 2H), 4.11 (t, *J*=6.6 Hz, 2H), 3.80 (s, 3H), 3.59 (t, *J*=7.0 Hz, 2H), 3.14 (t, *J*=6.6 Hz, 2H), 1.82 (t, *J*=7.0 Hz, 2H), 0.78 (m, 2H), 0.74 (m, 2H) ppm. LC/MS (ESI) 472.4 (M+H).

Following procedures analogous to that used for Part E and Part F of Example 1, but using the product of Example 225 as one of the starting materials, Examples 226-229 were prepared.

Example 226

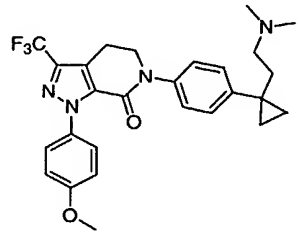
1-(4-Methoxy-phenyl)-6-{4-[1-(2-methylamino-ethyl)cyclopropyl]-phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



^{1}H NMR ($CDCl_3$) δ 7.45 (d, J=8.8 Hz, 2H), 7.26 (m, 4H), 6.91 (d, J=8.8 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, J=6.6 Hz, 2H), 2.98 (m, 2H), 2.75 (m, 6H), 1.97 (m, 2H), 0.86 (m, 2H), 0.79 (m, 2H) ppm. HRMS (ESI) calcd. 485.2165; found 485.2153 for $C_{26}H_{28}F_3N_4O_2$ (M+H). LC/MS (10-90% CH_3CN in H_2O in a 4-min run, t_R=2.10 min) 485.6 (M+H).

Example 227

6-{4-[1-(2-Dimethylamino-ethyl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt

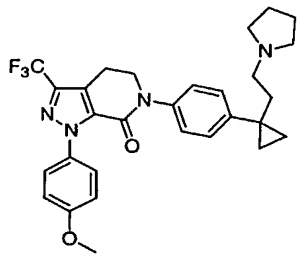


^{1}H NMR ($CDCl_3$) δ 7.45 (d, J=8.8 Hz, 2H), 7.26 (m, 4H), 6.91 (d, J=8.8 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, J=6.6 Hz, 2H), 2.98 (m, 2H), 2.75 (m, 6H), 1.97

(m, 2H), 0.86 (m, 2H), 0.79 (m, 2H) ppm. HRMS (ESI) calcd. 499.2322; found 499.2318 for $C_{27}H_{30}F_3N_4O_2$ (M+H). LC/MS (10-90% CH_3CN in H_2O in a 4-min run, t_R=2.10 min) 499.6 (M+H).

Example 228

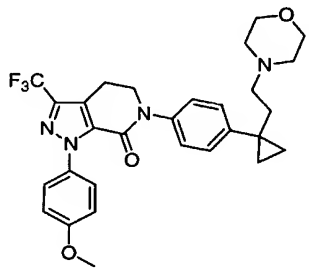
1-(4-Methoxy-phenyl)-6-{4-[1-(2-pyrrolidin-1-yl-ethyl)-cyclopropyl]-phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



^1H NMR ($CDCl_3$) δ 7.46 (d, J=8.8 Hz, 2H), 7.26 (m, 4H), 6.92 (d, J=8.8 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.77 (m, 2H), 3.16 (t, J=6.6 Hz, 2H), 3.02 (m, 2H), 2.65 (m, 2H), 2.02 (m, 6H), 0.84 (m, 2H), 0.77 (m, 2H). HRMS(ESI) calcd. 525.2478, found 525.2483 for $C_{29}H_{32}F_3N_4O_2$ (M+H). LC/MS (10-90% CH_3CN in H_2O in 4-min run, t_R=2.18 min) 525.6 (M+H).

Example 229

1-(4-Methoxy-phenyl)-6-{4-[1-(2-morpholin-4-yl-ethyl)-cyclopropyl]-phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt

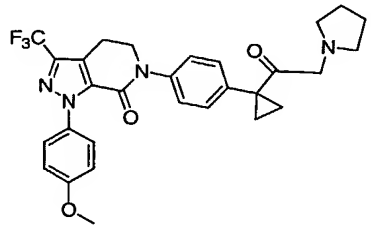


^1H NMR ($CDCl_3$) δ 7.45 (d, J=8.8 Hz, 2H), 7.26 (m, 4H), 6.92 (d, J=8.8 Hz, 2H), 4.12 (t, J=6.6 Hz, 2H), 3.93 (m, 4H), 3.81 (s, 3H), 3.47 (m, 2H), 3.16 (t, J=6.6 Hz, 2H), 2.98

(m, 2H), 2.72 (m, 2H), 1.99 (m, 2H), 0.85 (m, 2H), 0.76 (m, 2H) ppm. HRMS(ESI) calcd. 541.2427, found 541.2413 for $C_{29}H_{32}F_3N_4O_3$ (M+H). LC/MS (ESI) (10-90% CH_3CN in H_2O in a 4-min run, t_R=2.11 min), 541.6 (M+H).

Example 230

1-(4-Methoxy-phenyl)-6-{4-[1-(2-pyrrolidin-1-yl-acetyl)-cyclopropyl]-phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



Part A. 1-(4-Iodophenyl)-cyclopropanecarbonyl chloride (1.74 g, 5.69 mmol) was stirred in CH_3CN and THF (1:1 v/v, 20 mL) total at 0C under N_2. $TMSCHN_2$ (2M in hexanes, 4.3 mL) was added dropwise. The mixture was stirred at 0°C to rt for 2 h. It was partitioned between EtOAc and sat'd $NaHCO_3$. The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. HBr/HOAc (30%, 8 mL) was added dropwise to the residue at 0°C. The mixture was stirred at 0°C for 30 min, and EtOAc was added; it was washed with 15% citric acid, sat'd $NaHCO_3$, H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give crude 2-bromo-1-[1-(4-iodo-phenyl)-cyclopropyl]-ethanone (0.5 g).

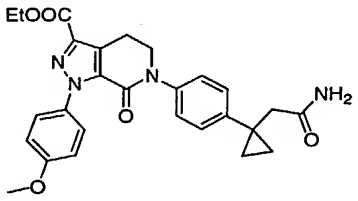
Part B. The product from Part A (0.5 g, 1.37 mmol) was dissolved in DMF (1.8 mL), a spatula tip of the K_2CO_3 and pyrrolidine (0.2 mL) were added. The mixture was heated at 80°C for 1.5 h. The cooled mixture was partitioned between EtOAc and H_2O. The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The

residue was purified by FCC (silica gel, EtOAc:CH_2Cl_2=0:1 to 1:0, then 10% MeOH in EtOAc) to give 1-[1-(4-iodo-phenyl)-cyclopropyl]-2-pyrrolidin-1-yl-ethanone (85 mg, yield: 17% for 2 steps). ^1H NMR ($CDCl_3$) δ 7.68 (d, *J*=8.4 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 3.30 (s, 2H), 2.51 (m, 4H), 1.75 (m, 4H), 1.63 (m, 2H) 1.10 (m, 2H) ppm. LC/MS (ESI) 356.4 (M+H).

Part C. The product of part B (50 mg, 0.14 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (52.5 mg, 0.17 mmoL) were stirred in DMSO (0.2 mL) in a Pyrex tube under N_2. K_2CO_3 (39 mg) was added followed by the addition of CuI (20 mg) and 9,10-phenantholine (20 mg). The mixture was stirred at 120°C for 2 h. The cooled mixture was purified by reverse phase HPLC to give the title compound (9.6 mg, yield: 12.7 %). LC/MS (ESI) 539.6 (M+H).

Example 231

6-[4-(1-Carbamoylmethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester



Part A. Following procedure similar to that of Part C in Example 220 but using 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester and [1-(4-iodo-phenyl)-cyclopropyl]-acetic acid tert-butyl ester as starting materials, 6-[4-(1-tert-butoxycarbonylmethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid ethyl ester was obtained (406.29

mg, yield: 86%). ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J*=8.9 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 6.91 (d, *J*=8.9 Hz, 2H), 4.47 (q, *J*=7.1 Hz, 2H), 4.12 (m, 2H), 3.81 (s, 3H), 3.32 (t, *J*=6.6 Hz, 2H), 2.50 (s, 2H), 1.44 (t, *J*=7.1 Hz, 3H), 1.38 (s, 9H), 0.90 (s, 4H) ppm. LRMS (ESI) 546.2 (M+H).

Part B. The product from Part A (450 mg) was stirred in a mixture of CH_2Cl_2 (10 mL) and TFA (15 mL) at rt for 4h. The solvents were evaporated. The residue was dried in vacuo to give 6-[4-(1-carboxymethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (386 mg, yield: 95.6%). ^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J*=8.7 Hz, 2H), 7.35 (d, *J*=8.3 Hz, 2H), 7.21 (d, *J*=8.3 Hz, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 4.47 (q, *J*=7.1 Hz, 2H), 4.14 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.34 (t, *J*=6.5 Hz, 2H), 2.65 (s, 2H), 1.43 (t, *J*=7.1 Hz, 3H), 0.97 (m, 2H), 0.91 (m, 2H) ppm. LRMS (ESI) 490.1 (M+H).

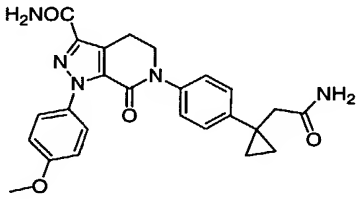
Part C. The product from Part B (150 mg, 0.31 mmol) was stirred in CH_2Cl_2 (5 mL). Oxalyl chloride (2M solution in CH_2Cl_2, 0.3 mL. ca. 2 eq) was added, followed by the addition of 1 drop of DMF. The mixture was stirred at rt for 1h. The solvents were evapoarated. The residue was dried in vaco. One third of the residue (0.1 mmol) was dissolved in THF (2.0 mL), concentrated $NH_3 \cdot H_2O$ (2.0 mL) was added. The mixture was stirred at rt for 2h. EtOAc was added. It was washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2, then EtOAc) to give pure title compound. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, *J*=8.9 Hz, 2H), 7.22 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.9 Hz, 2H), 5.46 (s, br, 1H), 5.30 (s, br, 1H), 4.38

(t, J=7.1 Hz, 2H), 4.03 (t, J=6.6 Hz, 2H), 3.73 (s, 3H), 3.23 (t, J=6.7 Hz, 2H), 2.45 (s, 2H), 1.36 (t, J=7.1 Hz, 2H), 0.88 (m, 4H) ppm. HRMS (ESI) $C_{27}H_{29}N_4O_5$ calcd for 489.2138, found 489.2152.

Following procedures analogous to that used for Example 231, Examples 232-238 were prepared.

Example 232

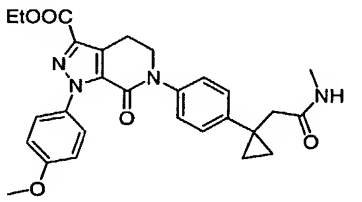
6-[4-(1-Carbamoylmethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



^{1}H NMR (methanol-d_4) δ 7.50 (d, J=8.9 Hz, 2H), 7.40 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.5 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 4.10 (t, J=6.6 Hz, 2H), 3.86 (s, 3H), 3.33 (m, 2H), 2.54 (s, 2H), 0.99 (m, 2H), 0.94 (m, 2H) ppm. LC/MS (ESI) t_R=2.66 min (10-90% MeOH in H_2O with 10 mM NH_4OAc in a 4-min gradient), 460.10 (M+H, 100%), 492.11 (M+H+MeOH, 70%).

Example 233

1-(4-Methoxy-phenyl)-6-[4-(1-methylcarbamoylmethyl-cyclopropyl)-phenyl]-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester

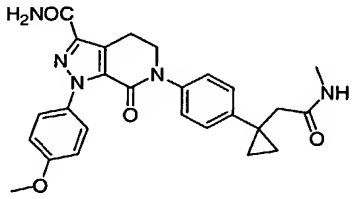


^{1}H NMR ($CDCl_3$) δ 7.39 (d, J=9.0 Hz, 2H), 7.17 (m, 4H), 6.82 (d, J=9.0 Hz, 2H), 5.46 (m, 1H), 4.38 (q, J=6.8 Hz, 2H), 4.02 (t, J=6.8 Hz, 2H), 3.73 (s, 3H), 3.23 (t, J=6.6 Hz,

2H), 2.61 (d, J=4.8 Hz, 3H), 2.43 (s, 2H), 1.36 (t, J=7.2 Hz, 3H), 0.87 (s, 4H) ppm. HRMS (ESI) $C_{28}H_{31}N_4O_5$, calcd for 503.2294, found 503.2281 .

Example 234

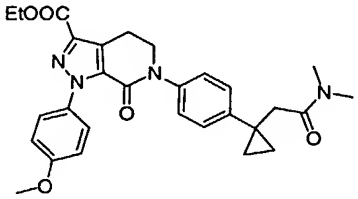
1-(4-Methoxy-phenyl)-6-[4-(1-methylcarbamoylmethyl-cyclopropyl)-phenyl]-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



^{1}H NMR (methanol-d_4) δ 7.38 (d, J=8.8 Hz, 2H), 7.23 (d, J=8.8 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 3.94 (t, J=6.6 Hz, 2H), 3.71 (s, 3H), 3.18 (t, J=6.6 Hz, 2H), 2.48 (s, 3H), 2.35 (s, 2H), 0.84 (m, 2H), 0.77 (m, 2H) ppm. LC/MS (ESI) t_R=2.76 min (10-90% MeOH in H_2O with 10 mM NH_4OAc in a 4-min gradient), 474.09 (M+H, 100%), 506.12 (M+H+MeOH, 100%).

Example 235

6-[4-(1-Dimethylcarbamoylmethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester

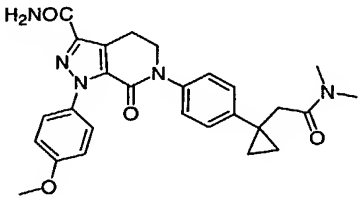


^{1}H NMR ($CDCl_3$) δ 7.40 (d, J=8.9 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 6.82 (d, J=9.0 Hz, 2H), 4.38 (q, J=7.1 Hz, 2H), 4.03 (t, J=6.6 Hz, 2H), 3.73 (s, 3H), 3.22 (t, J=6.6 Hz, 2H), 2.78 (s, 3H), 2.68 (s, 3H), 2.57 (s, 2H), 1.36 (t, J=7.1 Hz, 3H), 0.82 (m, 2H), 0.81 (m, 2H)

ppm. HRMS (ESI) $C_{29}H_{33}N_4O_5$, calcd for 517.2451, found 517.2439 .

Example 236

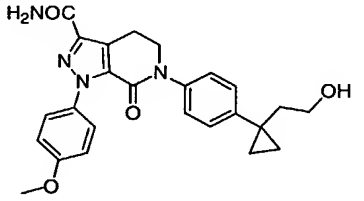
6-[4-(1-Dimethylcarbamoylmethyl-cyclopropyl)-phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



^{1}H NMR (methanol-d_4) δ 7.50 (d, J=9.0 Hz, 2H), 7.38 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 6.99 (d, J=9.0 Hz, 2H), 4.08 (t, J=6.6 Hz, 2H), 3.85 (s, 3H), 3.33 (m, 2H), 2.83 (s, 3H), 2.75 (s, 3H), 2.72 (s, 2H), 0.95 (m, 2H), 0.90 (m, 2H) ppm. LC/MS (ESI) t_R=2.90 min (10-90% MeOH in H_2O with 10 mM NH_4OAc in a 4-min gradient), 488.10 (M+H, 100%), 520.13 (M+H+MeOH, 60%).

Example 237

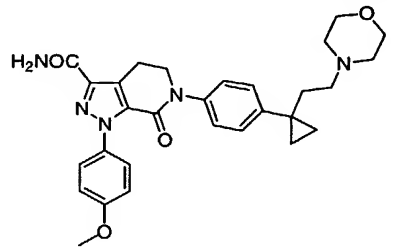
6-{4-[1-(2-Hydroxy-ethyl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



^{1}H NMR (methanol-d_4) δ 7.43 (d, J=8.8 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.5 Hz, 2H), 6.92 (d, J=8.9 Hz, 2H), 4.03 (m, 4H), 3.78 (s, 3H), 3.43 (t, J=6.6 Hz, 2H), 1.78 (t, J=7.0 Hz, 2H), 0.72 (m, 2H), 0.70 (m, 2H) ppm. LC/MS (ESI) t_R=2.62 min (10-90% MeOH in H_2O with 10 mM NH_4OAc in a 4-min gradient), 474.11 (M+H, 100%).

Example 238

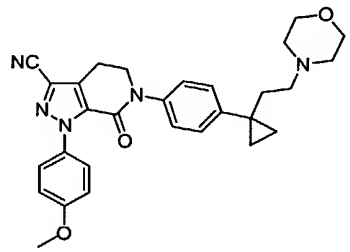
1-(4-Methoxy-phenyl)-6-{4-[1-(2-morpholin-4-yl-ethyl)-cyclopropyl]-phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



^{1}H NMR (methanol-d_4) δ 7.38 (d, J=9.0 Hz, 2H), 7.24 (d, J=8.5 Hz, 2H), 7.15 (d, J=8.5 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 3.97 (t, J=6.6 Hz, 2H), 3.73 (s, 3H), 3.52 (m, 4H), 3.20 (m, 2H), 2.25 (m, 6H), 1.70 (m, 2H), 0.70 (m, 2H), 0.65 (m, 2H) ppm. LC/MS (ESI) t_R=3.18 min (10-90% MeOH in H_2O with 10 mM NH_4OAc in a 4-min gradient), 516.13 (M+H, 100%).

Example 239

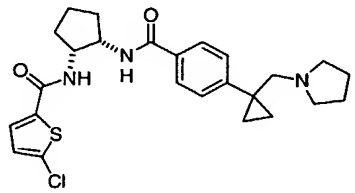
1-(4-Methoxy-phenyl)-6-{4-[1-(2-morpholin-4-yl-ethyl)-cyclopropyl]-phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following the procedure as Example 74 but using the product of Example 238 as the starting material, the titled compound was prepared. LRMS (ESI) 498.2 (M+H).

Example 240

(1*R*, 2*S*)-5-Chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclopentyl}-amide, trifluoroacetic acid salt



Part A. To a solution of (1*S*, 2*S*)-2-benzyloxy-cyclopentylamine (9.8 g, 51.2 mmol) in THF (150 mL) were sequentially added Et_3N (13.6 mL, 0.10 mol) and $(Boc)_2O$ (12.30 g, 56.4 mmol) at 0°C. The reaction mixture was stirred overnight at room temperature, and diluted with EtOAc (200 mL). The organic phase was washed with H_2O, brine, and dried (Na_2SO_4). The solvent was evaporated to afford (1*S*, 2*S*)-(2-benzyloxy-cyclopentyl)-carbamic acid tert-butyl ester (14.90 g, 100%) as a slight yellow solid. MS *m/z* 293.0 ($[M + H]^+$).

Part B. The product from Part A (10.0 mg, 34.2 mmol) was dissolved in ethanol (100 mL), Pd/C (800 mg, 5%) was then added. The reaction mixture was hydrogenated at 25 psi with stirring for 4 h, and filtered through a pad of Celite®. The filtrate was evaporated to afford (1*S*, 2*S*)-(2-hydroxy-cyclopentyl)-carbamic acid tert-butyl ester (6.84 g, 99%) as a white solid. MS *m/z* 202.0 ($[M + H]^+$).

Part C. To a solution of the product from Part B (4.95 g, 24.6 mmol) in CH_2Cl_2 (50 mL) were sequentially added Et_3N (4.11 mL, 29.51 mol) and MsCl (2.09 g, 27.05 mmol) at 0°C. The reaction mixture was stirred for 2 h at 0 °C, then quenched with H_2O and extracted with EtOAc (3 x 50 mL). The organic phase was washed with H_2O, brine, and dried (Na_2SO_4). The solvent was evaporated to afford (1*S*, 2*S*)-

methanesulfonic acid 2-tert-butoxycarbonylamino-cyclopentyl ester (6.35 g, 92%) as a white solid. MS *m/z* 297.0 ([M + NH_4]$^+$).

Part D. NaN_3 (4.40 g, 67.7 mmol) was added to a solution of the product from Part C (6.30 g, 22.6 mmol) in DMF (50 mL), and the reaction mixture was heated at 80 °C for 12 h with vigorous stirring. The reaction was cooled to room temperature, poured into water, and extracted with EtOAc (4 x 100 mL). The extracts were combined and washed with H_2O, aqueous LiCl (10%), brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was taken to next step without purification. The residue from above reaction was then dissolved in ethanol (200 mL), and Pd/C (300 mg, 5%) was added. The reaction mixture was hydrogenated at 1 atm with stirring for 24 h, and filtered through a pad of Celite®. The filtrate was evaporated to afford (1*S*, 2*R*)-(2-amino-cyclopentyl)-carbamic acid tert-butyl ester (6.84 g, 99%) as a white solid. MS *m/z* 201.0 ([M + H]$^+$).

Part E. The product from Part D (150 mg, 0.75 mmol) and 5-chloro-thiophene-2-carboxylic acid (101 mg, 0.62 mmol) were dissolved in DMF (2 mL) and cooled to 0°C. To this solution was added HATU (354 mg, 0.93 mmol), DIEA (0.22 mL, 1.24 mmol). The mixture was stirred overnight. It was diluted with ethyl acetate, washed with water, aqueous LiCl (10%), brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified on silica gel using 50% EtOAc-Hexane to afford (1*S*, 2*R*)-{2-[(5-chloro-thiophene-2-carbonyl)-amino]-cyclopentyl}-carbamic acid tert-butyl ester (115 mg, 54%) as a white solid. MS *m/z* 367.6 ([M+Na]$^+$).

Part F. The product from Part E (115 mg, 0.33 mmol) was suspended in CH_2Cl_2 (1 mL) and TFA (1 mL) was added. A

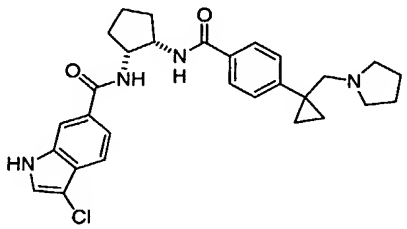
clear solution was obtained and stirred for 2 h at ambient temperature. The resulting solution was concentrated, and the residue was partitioned between EtOAc and aqueous Na_2CO_3. The aqueous was extracted with EtOAc (3 x 10 mL). The extracts were combined and washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded (1*R*, 2*S*)-5-chloro-thiophene-2-carboxylic acid (2-amino-cyclopentyl)-amide (80 mg, 98%) as a white solid that was taken to next step without purification. MS *m/z* 245.0 ($[M + H]^+$).

Part G. The product from Part F (40 mg, 0.16 mmol) and excess 4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl chloride (Example 1) and DIEA (0.05 mL) were stirred in CH_2Cl_2 (1 mL) at 0°C. The above solution was added Et_3N (0.05 mL) and stirred overnight. The reaction mixture was diluted with ethyl acetate, washed with water, aqueous LiCl (10%), brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified on reverse-phase HPLC to afford the title compound as a white solid. LRMS (ESI) 472.2 (M+H).

Using the same procedure as that described for Example 240, Examples 241-243 were prepared:

Example 241

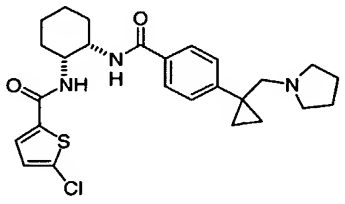
(1*R*, 2*S*)-3-Chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclopentyl}-amide, trifluoroacetic acid salt



LC/MS (ESI) 505.2 (M+H).

Example 242

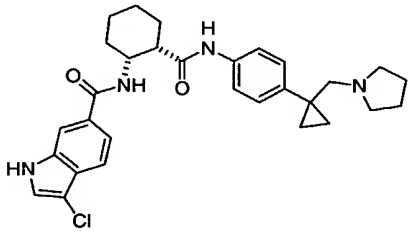
(1*R*, 2*S*)-5-Chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide, trifluoroacetic acid salt



LC/MS (ESI) 486.2 (M+H)

Example 243

Cis-3-Chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-phenylcarbamoyl]-cyclohexyl}-amide, trifluoroacetic acid salt



LRMS (ESI) 519.2 (M+H).

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of formula I:

$$P_4\text{-}P\text{-}M\text{-}M_4$$

I

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

M is a 3-10 membered carbocycle or a 4-10 membered heterocycle, consisting of: carbon atoms and 1-3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2;

ring M is substituted with 0-3 R^{1a} and 0-2 carbonyl groups, and there are 0-3 ring double bonds;

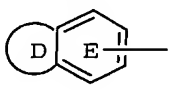
P is fused onto ring M and is a 5, 6, or 7 membered carbocycle or a 5, 6, or 7 membered heterocycle, consisting of: carbon atoms and 1-3 heteroatoms selected from O, $S(O)_p$, and N;

ring P is substituted with 0-3 R^{1a} and 0-2 carbonyl groups, and there are 0-3 ring double bonds;

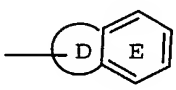
alternatively, ring P is absent and P_4 is directly attached to ring M, provided that when ring P is absent, P_4 and M_4 are attached to the 1,2, 1,3, or 1,4 positions of ring M;

one of P_4 and M_4 is -Z-A-B and the other $-G_1$-G, provided that P_4 and M_4 are attached to different rings when ring P is present;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

ring D is substituted with 0-2 R and there are 0-3 ring double bonds;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-3 R;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1-3 R;

alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1 R and with a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the 5-6 membered heterocycle is substituted with 0-2 carbonyls and 1-3 R and there are 0-3 ring double bonds;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $ONHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tC(O)H$, $(CR^8R^9)_tC(O)R^{2c}$, $(CR^8R^9)_tNR^7R^8$,

$(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7C(O)R^7$, $(CR^8R^9)_tOR^3$, $(CR^8R^9)_tS(O)_pNR^7R^8$, $(CR^8R^9)_tNR^7S(O)_pR^7$, $(CR^8R^9)_tSR^3$, $(CR^8R^9)_tS(O)R^3$, $(CR^8R^9)_tS(O)_2R^3$, and OCF_3, provided that $S(O)_pR^7$ forms other than $S(O)_2H$ or $S(O)H$;

alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

A is selected from:

C_{3-10} carbocycle substituted with 0-2 R^4, and

5-12 membered heterocycle substituted with 0-2 R^4 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

B is $Y-R^{4a}$ or $X-Y-R^{4a}$, provided that Z and B are attached to different atoms on A and A and R^{4a} or X and R^{4a} are attached to the same atom on Y;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1b})-$, $-CR^2(NR^{1b}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-S(O)_2NR^2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-CR^2R^{2a}NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-NR^2C(O)-$, $-C(O)NR^2-$, $-NR^2C(O)CR^2R^{2a}-$, $-C(O)NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2C(O)-$, $-CR^2R^{2a}C(O)NR^2-$, NR^2, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-OCR^2R^{2a}-$, and $-CR^2R^{2a}O-$;

Y is a C_{3-10} carbocycle or 3-10 membered heterocycle, wherein the carobocycle or heterocycle consists of carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, the carbocycle or heterocycle further

comprises 0-4 double bonds and 0-2 carbonyl groups, and the carbocycle or heterocycle is substituted with 0-2 R^4, provided that Y is other than a 1,3-dioxolanyl group;

alternatively, Y is CY^1Y^2, and Y^1 and Y^2 are independently C_{1-4} alkyl substituted with 0-2 R^4;

G_1 is absent or is selected from $(CR^3R^{3a})_{1-5}$, $(CR^3R^{3a})_{0-2}CR^3{=}CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C{\equiv}C(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(S)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}S(O)_2NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3e}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3bb}C(S)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(S)NR^{3b}(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^{3b}C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^{3b}S(O)_2(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uS(O)_2NR^{3b}C(O)NR^{3b}(CR^3R^{3a})_w$, wherein u + w total 0, 1, 2, 3, or 4, provided that G_1 does not form a N-

S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z is selected from a bond, $-(CR^3R^{3e})_{1-4}-$,
$(CR^3R^{3e})_qO(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qNR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qC(O)(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qC(O)O(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qOC(O)(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qC(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}C(O)(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qOC(O)O(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qOC(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}C(O)O(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}C(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qC(O)(CR^3R^{3e})_qC(O)(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}(CR^3R^{3e})_qC(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}C(O)(CR^3R^{3e})_qC(O)(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qC(O)(CR^3R^{3e})_qC(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}C(O)(CR^3R^{3e})_qC(O)NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qS(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qS(O)(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qS(O)_2(CR^3R^{3e})_{q1}$, $(CR^3R^{3e})_qSO_2NR^{3b}(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qNR^{3b}SO_2(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qS(O)NR^{3b}C(O)(CR^3R^{3e})_{q1}$,
$(CR^3R^{3e})_qC(O)NR^{3b}S(O)_2(CR^3R^{3e})_{q1}$, and
$(CR^3R^{3e})_qNR^{3b}SO_2NR^{3b}(CR^3R^{3e})_{q1}$, wherein q + q1 total 0, 1, 2, 3, or 4, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

provided that:

(a) when ring P is absent and ring M is a pyridyl ring, then Z is other than $C(O)NHCH_2$; and,

(b) when ring P is absent and ring M is a piperazinyl ring, then either Z is other than alkylene or A is other than phenyl;

Z^2 is selected from H, $S(O)_2NHR^{3b}$, $C(O)R^{3b}$, $C(O)NHR^{3b}$, $C(O)OR^{3f}$, $S(O)R^{3f}$, $S(O)_2R^{3f}$, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl$)-C_{3-10}$ carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)-5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{1a}, at each occurrence, is selected from H, $-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-CR^3R^{1b}R^{1b}$, $-(CR^3R^{3a})_r-O-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-NR^2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-S(O)_p-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-CO_2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-C(O)NR^2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-C(O)-(CR^3R^{3a})_r-R^{1b}$, $-C_{2-6}$ alkenylene-R^{1b}, $-C_{2-6}$ alkynylene-R^{1b}, and $-(CR^3R^{3a})_r-C(=NR^{1b})NR^3R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to adjacent atoms or to the same carbon atom, together with the atoms to which they are attached, they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, $-NO_2$, -CHO, $(CF_2)_rCF_3$, $(CR^3R^{3a})_rOR^2$, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, $CH(CH_2OR^2)_2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$,

$SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, $C(O)NR^2SO_2R^2$, C_{3-6} carbocycle substituted with 0-2 R^{4b}, and 5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond and provided that $S(O)_pR^2$ forms other than $S(O)_2H$ or S(O)H;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 3-6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy substituted with 0-2 R^{4b}, C_{1-6} alkyl substituted with 0-3 R^{4b}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4

heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2d}, at each occurrence, is selected from H, R^{4c}, C_{1-6} alkyl substituted with 0-2 R^{4c}, $-(CR^3R^{3a})_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4c}, and $-(CR^3R^{3a})_r$-5-10 membered heterocycle substituted with 0-2 R^{4c} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{2d} forms other than a N-halo, N-C-halo, $S(O)_p$-halo, O-halo, N-S, S-N, $S(O)_p$-$S(O)_p$, S-O, O-N, O-S, or O-O moiety;

alternatively, when two R^{2d}'s are attached to the same nitrogen atom, then R^{2d} and R^{2d}, together with the nitrogen atom to which they are attached, combine to form a 5-10 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2e}, at each occurrence, is selected from H, R^{4c}, C_{1-6} alkyl substituted with 0-2 R^{4c}, $-(CR^3R^{3a})_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4c}, and $-(CR^3R^{3a})_r$-5-10 membered heterocycle substituted with 0-2 R^{4c} and consisting of: carbon atoms and 1-4 heteroatoms selected from the

group consisting of N, O, and $S(O)_p$, provided that R^{2e} forms other than a C(O)-halo or $C(O)-S(O)_p$ moiety;

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

alternatively, R^3 and R^{3a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring consisting of: carbon atoms, the nitrogen atom to which R^3 and R^{3a} are attached, and 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3b}, at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

R^{3e}, at each occurrence, is selected from H, $S(O)_2NHR^3$, $C(O)R^3$, $C(O)NHR^3$, $C(O)OR^{3f}$, $S(O)R^{3f}$, $S(O)_2R^{3f}$, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3f}, at each occurrence, is selected from: C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, -(C_{0-4} alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and -(C_{0-4} alkyl)-5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{3g}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -$(CH_2)_r$-3-6 membered carbocycle, and -$(CH_2)_r$-5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

alternatively, when R^3 and R^{3g} are attached to the same carbon atom, they combine with the attached carbon atom to form a cyclopropyl group;

R^4, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NS(O)_2R^{5a})NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rC(O)NR^2C(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $(CR^3R^{3a})_rNR^2SO_2R^{5a}$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CR^3R^{3a})_r(CF_2)_rCF_3$, $N(CH_2)_rR^{1b}$, $O(CH_2)_rR^{1b}$, $S(CH_2)_rR^{1b}$, $(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $(CR^3R^{3a})_r$-5-6 membered heterocycle substituted with 0-1 R^5 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{4a} is selected from C_{1-6} alkyl substituted with 0-2 R^{4c}, C_{2-6} alkenyl substituted with 0-2 R^{4c}, C_{2-6} alkynyl substituted with 0-2 R^{4c}, $-(CR^3R^{3g})_r$-C_{5-10} membered carbocycle substituted with 0-3 R^{4c}, $-(CR^3R^{3g})_r$-5-10 membered heterocycle substituted with 0-3 R^{4c} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, $(CR^3R^{3g})_rCN$, $(CR^3R^{3g})_rC(=NR^{2d})NR^{2d}R^{2d}$, $(CR^3R^{3g})_rNR^{2d}C(=NR^{2d})NR^{2d}R^{2d}$, $(CR^3R^{3g})_rNR^{2d}C(R^{2e})(=NR^{2d})$, $(CR^3R^{3g})_rNR^{2d}R^{2d}$, $(CR^3R^{3g})_rN(\rightarrow O)R^{2d}R^{2d}$, $(CR^3R^{3g})_rOR^{2d}$, $(CR^3R^{3g})_r$-$NR^{2d}C(O)R^{2e}$, $(CR^3R^{3g})_r$-$C(O)R^{2e}$, $(CR^3R^{3g})_r$-$OC(O)R^{2e}$, $(CR^3R^{3g})_r$-$C(O)NR^{2d}R^{2d}$, $(CR^3R^{3g})_r$-$C(O)OR^{2d}$, $(CR^3R^{3g})_r$-$NR^{2d}C(O)NR^{2d}R^{2d}$, $(CR^3R^{3g})_r$-$OC(O)NR^{2d}R^{2d}$, $(CR^3R^{3g})_r$-$NR^{2d}C(O)OR^{2d}$, $(CR^3R^{3g})_r$-$SO_2NR^{2d}R^{2d}$, $(CR^3R^{3g})_r$-$NR^{2d}SO_2NR^{2d}R^{2d}$,

$(CR^3R^{3g})_r$-C(O)$NR^{2d}SO_2R^{2d}$, $(CR^3R^{3g})_r$-$NR^{2d}SO_2R^{2d}$, and $(CR^3R^{3g})_r$-S(O)$_pR^{2d}$, provided that S(O)$_pR^{2d}$ forms other than S(O)$_2$H or S(O)H and further provided that R^{4a} is other than a hydroxamic acid;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_r$-C(O)NR^3R^{3a}, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_r$-C(=NR^3)NR^3R^{3a}, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, and $(CH_2)_r(CF_2)_rCF_3$;

R^{4c}, at each occurrence, is selected from =O, $(CR^3R^{3a})_rOR^2$, $(CR^3R^{3a})_rF$, $(CR^3R^{3a})_rBr$, $(CR^3R^{3a})_rCl$, $(CR^3R^{3a})_rCF_3$, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rN(\rightarrow O)R^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rN$=CHOR^3, $(CR^3R^{3a})_rC(O)NR^2(CH_2)_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(=NR^2)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rC(O)NR^2SO_2$-$C_{1-4}$ alkyl, $(CR^3R^{3a})_rNR^2SO_2R^{5a}$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CF_2)_rCF_3$, $(CR^3R^{3a})_rC_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $(CR^3R^{3a})_r$4-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S(O)$_p$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CH_2)_rNR^3C(O)NR^3R^{3a}$, $(CH_2)_rCH(=NOR^{3d})$, $(CH_2)_rC(=NR^3)NR^3R^{3a}$, $(CH_2)_rNR^3C(=NR^3)NR^3R^{3a}$, $(CH_2)_rSO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2NR^3R^{3a}$, $(CH_2)_rNR^3SO_2$-C_{1-4} alkyl, $(CH_2)_rNR^3SO_2CF_3$, $(CH_2)_rNR^3SO_2$-phenyl, $(CH_2)_rS(O)_pCF_3$, $(CH_2)_rS(O)_p$-C_{1-4} alkyl, $(CH_2)_rS(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^{5a}, at each occurrence, is selected from C_{1-6} alkyl, $(CH_2)_rOR^3$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $(CH_2)_rNR^3C(O)R^{3a}$, $(CH_2)_rC(O)NR^3R^{3a}$, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6, provided that R^{5a} does not form a S-N or $S(O)_p$-C(O) bond;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkyl-C(O)-, C_{1-6} alkyl-O-, $(CH_2)_n$-phenyl, C_{1-4} alkyl-OC(O)-, C_{6-10} aryl-O-, C_{6-10} aryl-OC(O)-, C_{6-10} aryl-CH_2-C(O)-, C_{1-4} alkyl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{6-10} aryl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{1-6} alkyl-NH_2-C(O)-, phenyl-NH_2-C(O)-, and phenyl C_{1-4} alkyl-C(O)-;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-10 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

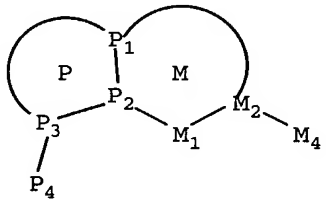
n, at each occurrence, is selected from 0, 1, 2, and 3;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, and 6; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

2. A compound according to Claim 1, wherein the compound is of Formula II:



II

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

ring M, including P_1, P_2, M_1, and M_2, is a 5, 6, or 7 membered carbocycle or a 5, 6, or 7 membered

heterocycle, consisting of: carbon atoms and 1-3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2;

ring M is substituted with 0-2 R^{1a} and 0-2 carbonyl groups, and there are 0-3 ring double bonds;

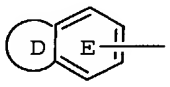
ring P, including P_1, P_2, and P_3, is a 5 or 6 membered aromatic heterocycle, consisting of: carbon atoms and 1-3 heteroatoms selected from O, $S(O)_p$, and N;

alternatively, ring P, including P_1, P_2, and P_3, is a 5 or 6 membered dihydro-aromatic heterocycle, consisting of: carbon atoms and 1-3 heteroatoms selected from O, $S(O)_p$, and N;

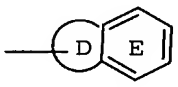
ring P is substituted with 0-2 R^{1a};

one of P_4 and M_4 is -Z-A-B and the other $-G_1$-G;

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

ring D is substituted with 0-2 R and there are 0-3 ring double bonds;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-3 R;

alternatively, ring D is absent, and ring E is selected from phenyl, pyridyl, pyrimidyl, and thienyl, and ring E is substituted with 1-3 R;

alternatively, ring D is absent, ring E is selected from phenyl, pyridyl, and thienyl, and ring E is substituted with 1 R and substituted with a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the 5-6 membered heterocycle is substituted with 0-2 carbonyls and 1-3 R and there are 0-3 ring double bonds;

R is selected from H, C_{1-4} alkyl, F, Cl, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, CN, $C(=NH)NH_2$, $C(=NH)NHOH$, $C(=NH)NHOCH_3$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $C(O)NR^7R^8$, $CH_2C(O)NR^7R^8$, $S(O)_pNR^7R^8$, $CH_2S(O)_pNR^7R^8$, SO_2R^3, and OCF_3;

alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

A is selected from:

C_{5-10} carbocycle substituted with 0-2 R^4, and

5-10 membered heterocycle substituted with 0-2 R^4 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_2-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2-$, $-NR^2S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2-$, NR^2, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-OCR^2R^{2a}-$, and $-CR^2R^{2a}O-$;

Y is a C_{3-7} monocyclic carbocycle or 3-7 membered monocyclic heterocycle, wherein the carobocycle or heterocycle consists of: carbon atoms and 0-2 heteroatoms selected from N, O, and S(O)p, the carbocycle or heterocycle further comprises 0-2 double bonds and 0-2 carbonyl groups, and the carbocycle or heterocycle is substituted with 0-2 R^4;

alternatively, Y is CY^1Y^2, and Y^1 and Y^2 are independently C_{1-3} alkyl substituted with 0-1 R^4;

Z is selected from a bond, CH_2, CH_2CH_2, CH_2O, OCH_2, C(O), NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $NHC(O)CH_2C(O)NH$, $S(O)_2$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^2 is selected from H, C_{1-4} alkyl, phenyl, benzyl, $C(O)R^{3b}$, $S(O)R^{3f}$, and $S(O)_2R^{3f}$;

R^{1a}, at each occurrence, is selected from H, $-(CH_2)_r-R^{1b}$, $-(CH(CH_3))_r-R^{1b}$, $-(C(CH_3)_2)_r-R^{1b}$, $-O-(CR^3R^{3a})_r-R^{1b}$, $-NR^2-(CR^3R^{3a})_r-R^{1b}$, and $-S-(CR^3R^{3a})_r-R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

alternatively, when two R^{1a} groups are attached to adjacent atoms or to the same carbon atom, together with the atoms to which they are attached, they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double ring bonds;

R^{1b} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, F, Cl, Br, I, -CN, -CHO, CF_3, OR^2, NR^2R^{2a}, $C(O)R^{2b}$, CO_2R^{2b}, $OC(O)R^2$, CO_2R^{2a}, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^2$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^2R^{2a}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^2$, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond and provided that $S(O)_pR^2$ forms other than $S(O)_2H$ or S(O)H;

R^2, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, a C_{5-6} carbocycle-CH_2- substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated

ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2d}, at each occurrence, is selected from H, R^{4c}, C_{1-4} alkyl substituted with 0-2 R^{4c}, $-(CR^3R^{3a})_r-C_{3-6}$ carbocycle substituted with 0-2 R^{4c}, and $-(CR^3R^{3a})_r$-5-6 membered heterocycle substituted with 0-2 R^{4c} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{2d} forms other than a N-halo, N-C-halo, $S(O)_p$-halo, O-halo, N-S, S-N, $S(O)_p$-$S(O)_p$, S-O, O-N, O-S, or O-O moiety;

alternatively, when two R^{2d}'s are attached to the same nitrogen atom, then R^{2d} and R^{2d}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated

or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{2e}, at each occurrence, is selected from H, R^{4c}, C_{1-4} alkyl substituted with 0-2 R^{4c}, $-(CR^3R^{3a})_r-C_{3-6}$ carbocycle substituted with 0-2 R^{4c}, and $-(CR^3R^{3a})_r$-5-6 membered heterocycle substituted with 0-2 R^{4c} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{2e} forms other than a C(O)-halo or $C(O)-S(O)_p$ moiety;

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

alternatively, R^3 and R^{3a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring consisting of: carbon atoms and the nitrogen atom to which R^3 and R^{3a} are attached;

R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2-phenyl, CH_2CH_2-phenyl, and $C(=O)R^{3c}$;

R^{3g}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, cyclopropyl, cyclopropyl-methyl, benzyl, and phenyl;

alternatively, when R^3 and R^{3g} are attached to the same carbon atom, they combine with the attached carbon atom to form a cyclopropyl group;

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, $(CH_2)_2OR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^{5a}$, CF_3, CF_2CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered heterocycle substituted with 0-1 R^5 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{4b}, at each occurrence, is selected from H, =O, OR^3, CH_2OR^3, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, CH_2-$C(O)R^3$, $C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $CH_2NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $CH_2C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH_2NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $CH_2C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $CH_2NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $CH_2SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $CH_2NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $CH_2NR^3SO_2$-C_{1-4} alkyl, $NR^3SO_2CF_3$, $CH_2NR^3SO_2CF_3$, NR^3SO_2-phenyl, $CH_2NR^3SO_2$-phenyl, $S(O)_pCF_3$, $CH_2S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $CH_2S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $CH_2S(O)_p$-phenyl, CF_3, and CH_2-CF_3;

R^{4c}, at each occurrence, is selected from =O, $(CR^3R^{3a})_rOR^2$, $(CR^3R^{3a})_rF$, $(CR^3R^{3a})_rBr$, $(CR^3R^{3a})_rCl$, $(CR^3R^{3a})_rCF_3$, C_{1-4}

alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, $(CR^3R^{3a})_rCN$, $(CR^3R^{3a})_rNO_2$, $(CR^3R^{3a})_rNR^2R^{2a}$, $(CR^3R^{3a})_rN(\rightarrow O)R^2R^{2a}$, $(CR^3R^{3a})_rC(O)R^{2c}$, $(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $(CR^3R^{3a})_rNR^2SO_2R^{5a}$, $(CR^3R^{3a})_rS(O)_pR^{5a}$, $(CF_2)_rCF_3$, $(CR^3R^{3a})_rC_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $(CR^3R^{3a})_r$5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

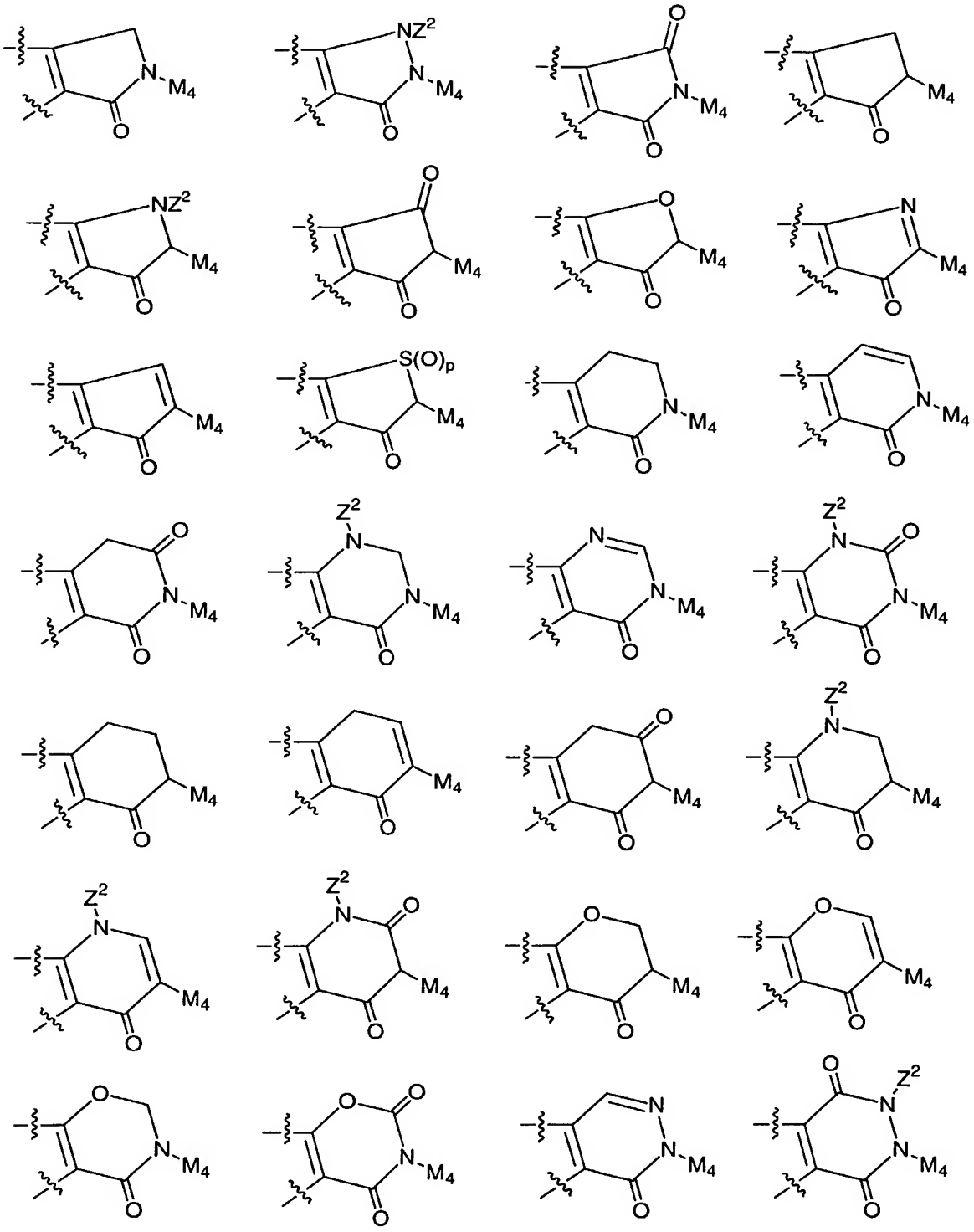
R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, OR^3, CH_2OR^3, F, Cl, -CN, NO_2, NR^3R^{3a}, $CH_2NR^3R^{3a}$, $C(O)R^3$, $CH_2C(O)R^3$, $C(O)OR^{3c}$, $CH_2C(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

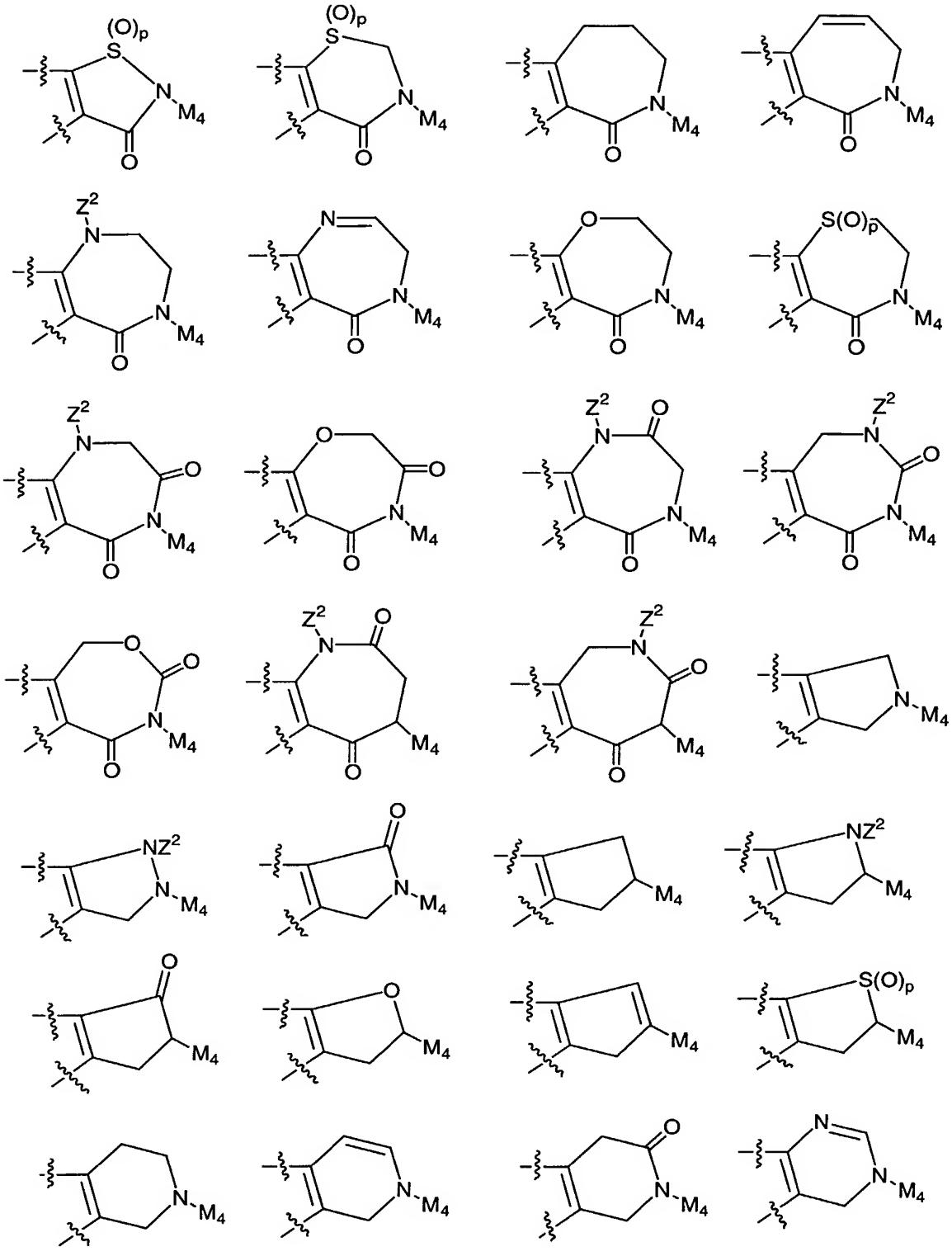
R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl; and,

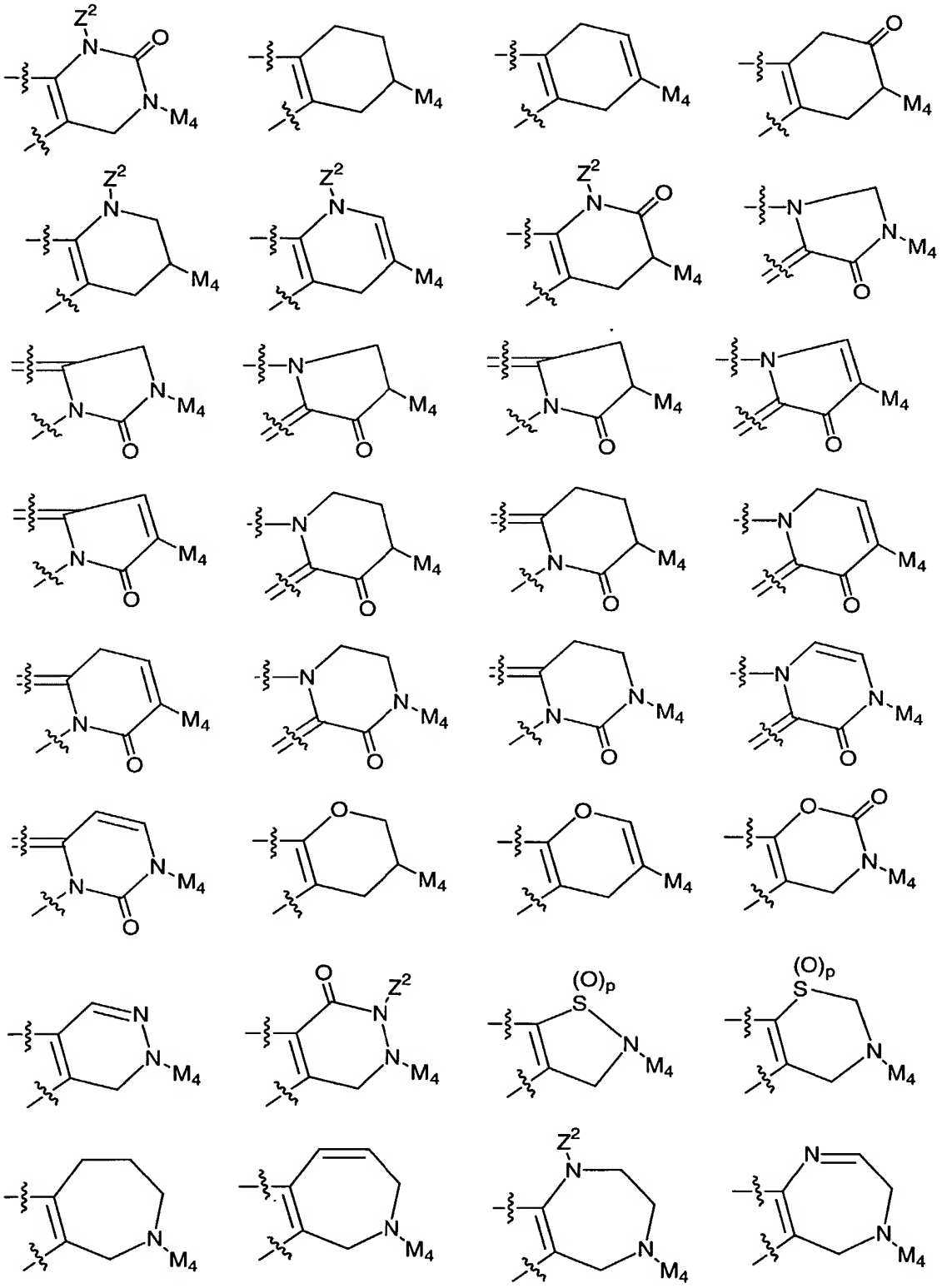
r, at each occurrence, is selected from 0, 1, 2, and 3.

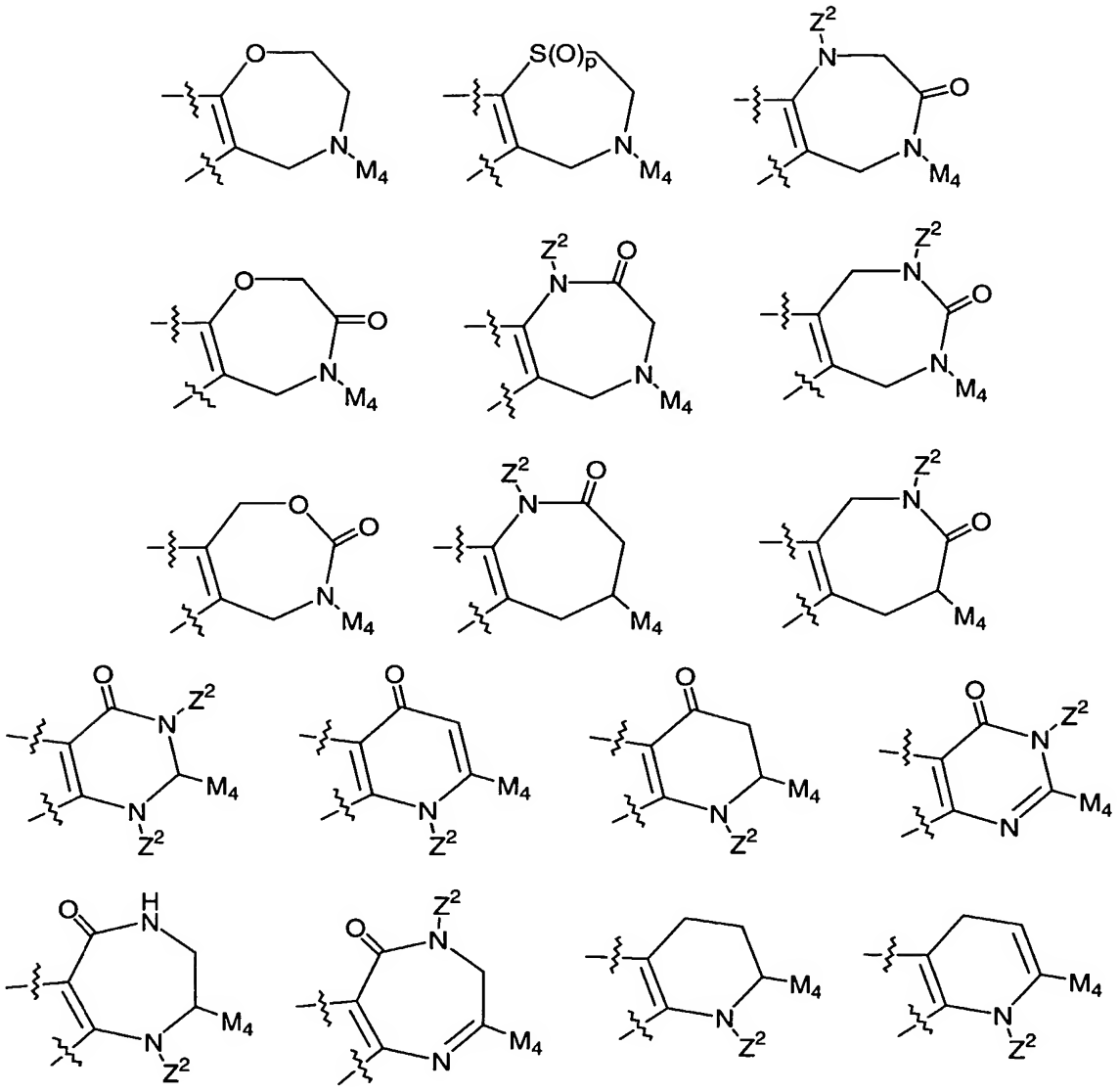
3. A compound according to Claim 2, wherein:

ring M is substituted with 0-2 R^{1a} and is selected from the group:



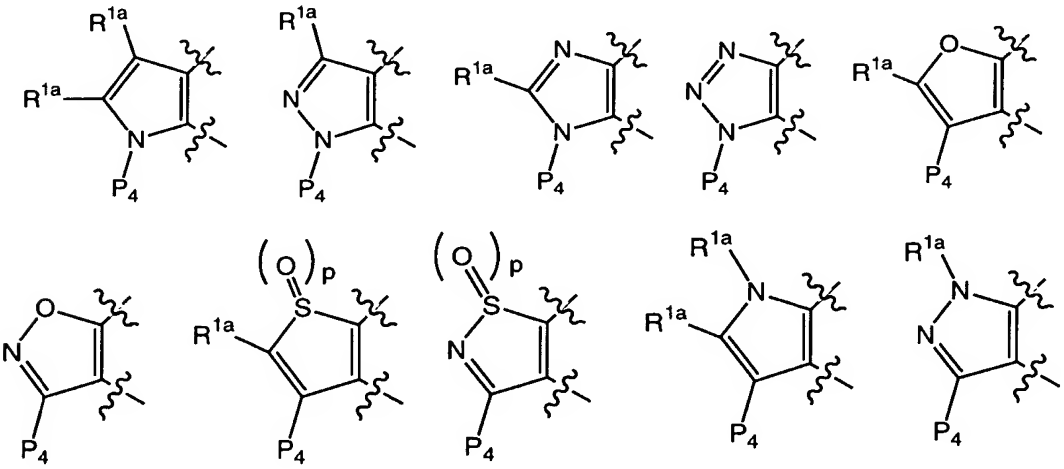


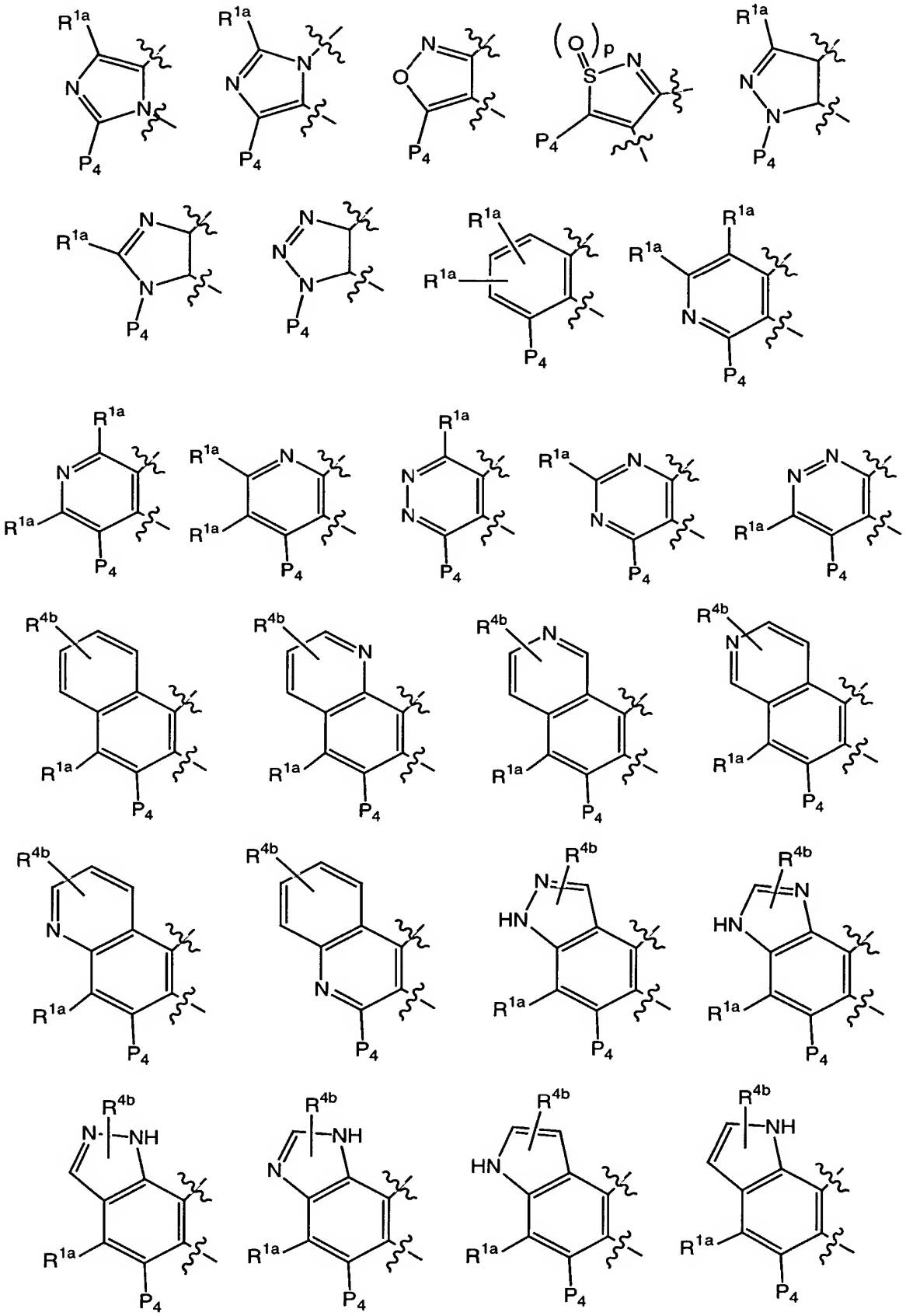


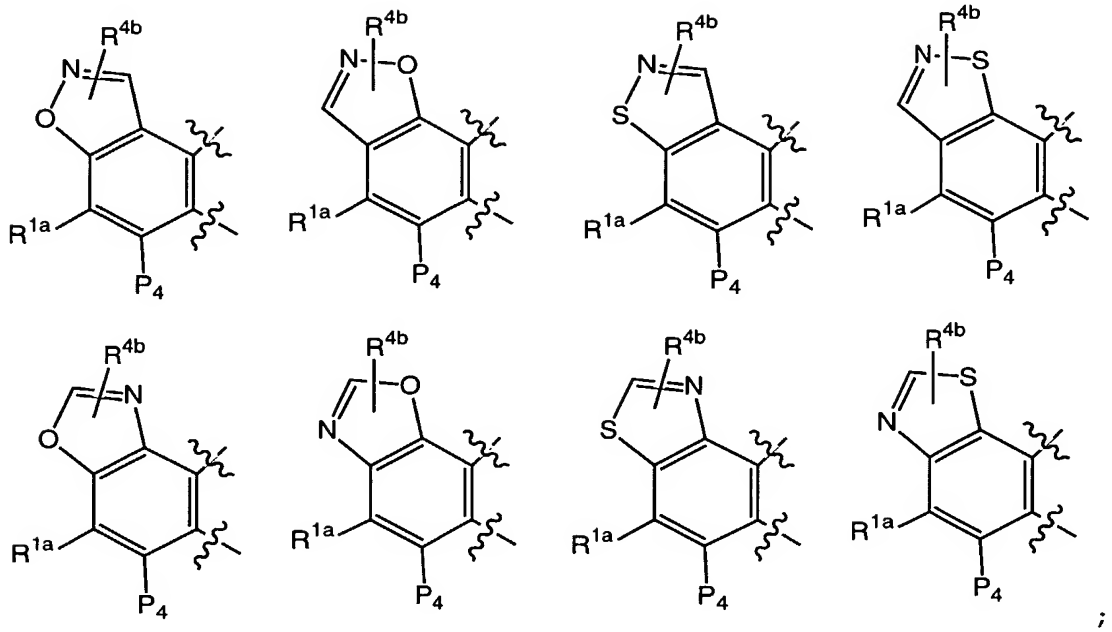


;

ring P, including P_1, P_2, P_3, and P_4 is selected from group:







;

G is selected from the group:

phenyl; 2,5-bis-aminomethyl-phenyl;
2-amido-4-methoxy-phenyl; 2-amido-5-chloro-phenyl;
2-amido-phenyl; 2-aminomethyl-3-fluoro-phenyl;
2-aminomethyl-3-methoxy-phenyl;
2-aminomethyl-4-fluoro-phenyl;
2-aminomethyl-4-methoxy-phenyl;
2-aminomethyl-5-fluoro-phenyl;
2-aminomethyl-5-methoxy-phenyl;
2-aminomethyl-6-fluoro-phenyl; 2-aminomethyl-phenyl;
2-amino-pyrid-4-yl; 2-aminosulfonyl-4-methoxy-phenyl;
2-aminosulfonyl-phenyl; 2-aminomethyl-4-ethyl-phenyl; 2-aminosulfonyl-4-ethyl-phenyl; 2-amido-4-ethyl-phenyl;
2-hydroxy-4-methoxy-phenyl; 2-methylsulfonyl-phenyl;
3-(N,N-dimethylamino)-4-chloro-phenyl;
3-(N,N-dimethylamino)-phenyl; 3-(N-hydroxy-amidino)-phenyl;
3-(N-methoxy-amidino)-phenyl;
3-(N-methylamino)-4-chloro-phenyl;
3-(N-methylamino)-phenyl; 3-amidino-phenyl;
3-amido-6-hydroxy-phenyl; 3-amido-phenyl;
3-amino-4-chloro-phenyl; 3-aminomethyl-phenyl;
3-amino-phenyl; 3-chloro-4-fluoro-phenyl; 3-chloro-phenyl;